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약학석사학위논문

**Amide Acetal을 활용한 팔라듐 매개  
Allylation 연구**

**Palladium-Catalyzed Allylation using Amide Acetal**

2018년 2월

서울대학교 대학원

약학과 약품화학 전공

정 재 현

## 국문 초록

팔라듐 매개 allylation은 탄소 원자간 또는 탄소 원자와 헤테로 원자간 결합을 형성하는 효율적인 합성법이다. Tsuji-Trost reaction으로도 알려진 이 반응은 다양한 응용 방법과 반응에 사용할 수 있는 알릴 기질들이 연구되었다. 기질 중 알릴 알코올은 히드록시기의 약한 leaving ability로 인해 알릴원 (allyl source)으로서 잘 사용되지 못했다. 그 대신 알코올을 halides, acetates, carbonates으로 유도체화하거나 특정 리간드, 루이스 산 등으로 히드록시기를 활성화시켜 특정한 화합물에서 제한적으로 사용되었다.

본 연구진은 amide acetal을 통해 알릴 알코올의 히드록시기를 *in situ*로 활성화하는 방법을 이용하여 알릴 화합물을 합성하였다. amide acetal로서 *N,N*-dimethylacetamide dimethyl acetal (DMADA)을 사용하여 알릴 알코올을 활성화시켰고, 팔라듐 촉매 ( $\text{Pd}(\text{PPh}_3)_4$ )와 다양한 친핵체들을 적용하여 allylation 반응을 진행하였다. 개발된 반응을 통해 온화한 조건에서 높은 수율로 알릴 화합물을 얻을 수 있었고, 탄소 친핵체 뿐만 아니라 질소 또는 산소 친핵체에서의 합성도 성공적으로 수행하였다. 추가적으로 반응 속도법 분석을 통해 개발된 반응의 기전을 연구하였다.

**주요어** : Amide acetal, Palladium, Synthetic methods

**학 번** : 2016 – 21827

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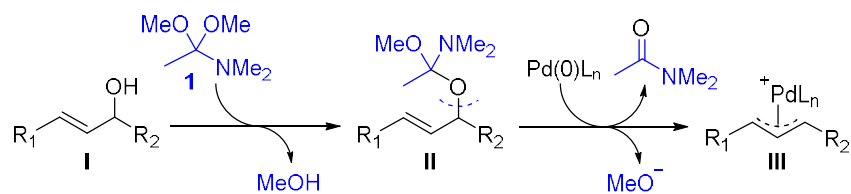
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## I. Introduction

팔라듐 매개 allylation (Tsuji-Trost reaction)은 탄소-탄소 결합과 탄소-헤테로 원자 결합을 형성하는 효율적인 합성법이다.<sup>1</sup> 지금까지 이 반응의 다양한 응용법이 연구되었고, 반응에 적용할 수 있는 알릴 기질들도 연구되었다.<sup>2</sup> 팔라듐 촉매와 알릴 기질이  $[Pd(\eta^3\text{-allyl})]$  complex를 형성하는 것이 반응의 핵심기전으로 잘 알려져 있다. 하지만, 기질 중 알릴알코올은 히드록시기의 약한 leaving ability로 인해 알릴원 (allyl source)으로서 잘 사용되지 못했다. 그 대신 히드록시기를 halides, acetates, carbonates 등의 좋은 이탈기로 유도체화하여 반응에 사용했으나, 사용될 알릴 알코올을 반응 전에 전처리하는 단점이 있었다. 이런 단계적 손실 때문에 히드록시기의 leaving ability를 직접적으로 증가시켜 주는 반응의 개발은 절실했다.<sup>3</sup> 하지만, 이런 반응들은 특정한 리간드를 요구하거나 harsh한 활성화제 (activator)가 반응상에서 투입되어 *in situ* activation를 거쳐야했다.<sup>2,4-6</sup> 이런 활성화제들은 대부분 루이스 산이나 브뢴스테드 산이기에<sup>2e-g,6</sup> 산성에 민감한 관능기에 사용되기 어렵다.  $As_2O_3$ ,  $B_2O_3$ ,  $CO_2$  gas와 같은 몇몇 물질들은 히드록시기와 공유결합을 형성하나 그 효율이 상대적으로 떨어진다.<sup>2,7</sup>

활성제들은 팔라듐 매개 allylation 반응에서 알릴 알코올을 활성화할 수 있음에도 불구하고, 산성 같은 특성으로 인해 다양한 화합물의 사용에 있어서는 제약이 있다. 오직 소수의 활성화제들이나 특정 조건에서의 반응들만 탄소와 질소 친핵체들이 사용되었다.<sup>5a,c,7d</sup> 따라서 본 연구진은 amide acetal을 통해 알릴 알코올의 히드록시기를 *in situ*로 활성화하는 방법을 이용하여 알릴 화합물을 합성하기로 했다 (Scheme 1). amide acetal을 활용한 allylation 반응은 온화하고 중성적인 반응 조건이기에 탄소나 다른 헤테로 원자 친핵체에 대해서도 광범위하게 적용이 가능한 효율적인 반응이다.

Scheme 1. amide acetal을 활용한 팔라듐 매개 allylation 반응에서의 활성화.



## II. Results and Discussion

다른 orthoester 와 다르게 amide acetal 인 *N,N*-dimethylacetamide dimethyl acetal (DMADA, **1**)은 중성적인 조건에서 trans-acetalization 이 일어난다.<sup>8,9</sup> 우리는 이런 점을 착안하여 히드록시기 활성화를 통해 팔라듐 매개 allylation 반응을 진행하기로 하였다. 알릴 알코올 **I** 과 DMADA 의 trans-acetalization 을 통해서 생성되는 allyl acetal **II** 에 팔라듐 촉매가 결합하여  $[Pd(\eta^3\text{-allyl})]$  intermediate **III** 을 형성한다. 이런 과정을 통해 DMADA 가 알릴 알코올의 히드록시기와 반응할 때, 엔트로피적 측면에서 *N,N*-dimethylacetamide (DMA)와 methanol 을 형성한다.

이 연구를 진행하기 위해 모델 친핵체로 diethyl methylmalonate (**3a**, Table 1)을 적용하여 amide acetal 로 알릴 알코올을 활성화시킨 뒤 반응을 진행하였다. **3a** 와 allyl alcohol **2a** (2 equiv)가 DMADA 와 함께 반응할 때, 알릴 화합물 **4aa** 은 형성되지 않았다. 심지어 장기간 높은 온도에서 반응을 진행시켰지만 반응이 진행되지 않았다. 팔라듐 촉매를 첨가할 때야 원하는 물질을 얻을 수 있었다.<sup>10</sup> 최적화된 반응 조건을 얻기 위해서 여러가지 조건으로 반응을 탐색하였다. 실험을 통해 우린 acetonitrile 을 용매로 사용했을 때 palladium complex 가 잘 형성되며, 팔라듐 촉매로 tetrakis(triphenylphosphine) palladium(0) ( $Pd(PPh_3)_4$ )가 반응성이 우수하다는 것을 알았다. 반응 조건이 50 °C 일 때 **4aa** 가 1 시간만에 97% 수율로 형성되었다 (Table 1, entry 1). 다른 팔라듐 촉매들은 활성이 떨어지거나 (Table 1, entries 2-6) 높은 수율로 product 를 얻기 위해 phosphine ligand 를 따로 추가해줘야 했다 (Table 1, entries 7-9). *N,N*-dimethylformamide (DMF)와 tetrahydrofuran (THF)같은 극성 용매에서 높은 수율이 나타났지만 (Table 1, entries 10 and 11), 다른 비극성 용매에서는 낮은 수율을 보여주었다 (Table 1, entries 12 and 13). allyl alcohol **2a** 를 줄어든 용량 (1 equiv)을 사용하여 반응을 하면, 반응이 12 시간이 지나도 완결나지 않고 **4aa** 의 수율도

42% 밖에 되지 않았다 [97% based on recovered starting material (brsm)]. 이것은 아무래도 **2a** 의 낮은 끓는 점 때문인 것으로 생각된다 (Table 1, entry 14). 반면에, sealed vial 에서는 2 시간만에 반응이 완결되었다 (Table 1, entry 15). 이런 반응에서 **3a** 의 methylene group 을 탈수소하기 위한 염기나, 알릴 알코올을 활성화시키기 위한 산도 필요가 없다.

Table 1. 팔라듐 매개 allylation 반응 조건 최적화<sup>a</sup>

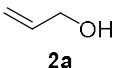
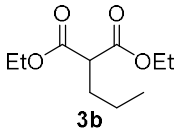
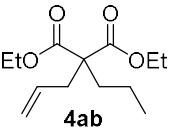
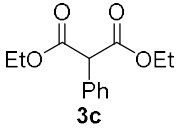
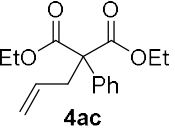
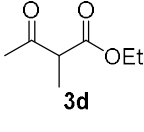
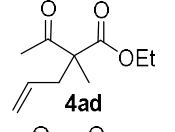
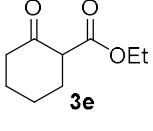
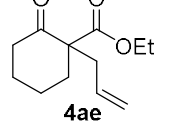
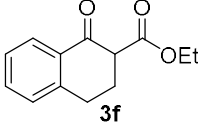
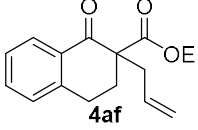
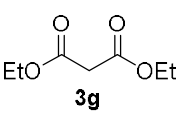
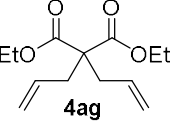
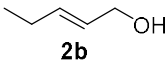
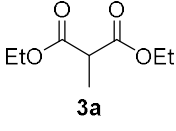
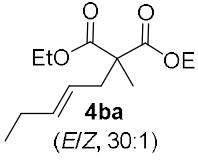
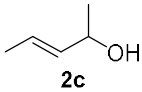
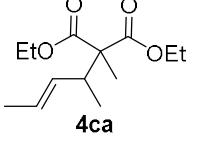
Entry	Pd catalyst	Additive	Solvent	Time [h]	Yield [%] <sup>b</sup>
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	MeCN	1	97
2	Pd(dba) <sub>2</sub> <sup>c</sup>	-	MeCN	12	32 (87) <sup>d</sup>
3	Pd(dba) <sub>3</sub> ·CHCl <sub>3</sub>	-	MeCN	12	29 (51) <sup>d</sup>
4	[PdCl <sub>2</sub> (C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> ]	-	MeCN	12	30 (34) <sup>d</sup>
5	PdCl <sub>2</sub>	-	MeCN	12	23 (51) <sup>d</sup>
6	Pd(OAc) <sub>2</sub>	-	MeCN	12	34 (92) <sup>d</sup>
7	Pd(dba) <sub>2</sub>	PPh <sub>3</sub>	MeCN	12	85
8	Pd(dba) <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	MeCN	12	94
9	[PdCl <sub>2</sub> (C <sub>3</sub> H <sub>5</sub> ) <sub>2</sub> ]	PPh <sub>3</sub>	MeCN	12	89
10	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	DMF	5	94
11	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	THF	12	89
12	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	DCE <sup>c</sup>	12	60
13	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	PhMe	12	45
14 <sup>e</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	MeCN	12	42 (97) <sup>d</sup>

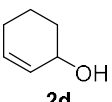
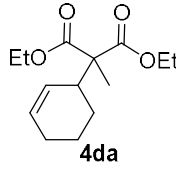
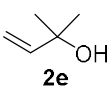
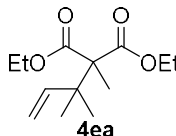


15 <sup>f</sup>	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	MeCN	2	93
<sup>a</sup> Reagents and conditions: <b>2a</b> (2 mmol), <b>3a</b> (1 mmol), Pd catalyst (0.05 mmol), additive (0.1 mmol), DMADA (2 mmol), solvent (2 mL). <sup>b</sup> Yield determined by <sup>1</sup> H NMR analysis using dibromomethane as the internal standard. <sup>c</sup> dba = dibenzylideneacetone and DCE = 1,2-dichloroethane. <sup>d</sup> Numbers in parentheses indicate yield based on the recovered starting material <b>3a</b> . <sup>e</sup> Reaction employed 1 mmol of <b>2a</b> . <sup>f</sup> Reaction was performed in a sealed vial.					

적용 가능한 기질들의 범위를 알아보기 위해, 위에 설정된 조건 (Table 1, entry 1)에서 다양한 알릴 알코올들 **2a-2e** 과 dicarbonyl compounds **3a-3g** 를 반응에 사용했었다 (Table 2). 2-methyl malonate **3a** 와 같이 프로필기와 페닐기가 치환된 **3b** 와 **3c** 에서도 1 시간만에 생성물 **4ab** 와 **4ac** 를 높은 수율로 얻을 수 있었다 (Table 2, entries 1 and 2). keto ester **3d** 도 성공적으로 allylation 이 진행되어 **4ad** 가 형성되었고 (Table 2, entry 3), cyclic keto ester **3e** 와 **3f** 도 역시 훌륭하게 합성되었다 (Table 2, entries 4 and 5). 적용된 반응 조건에서 치환기가 없는 dicarbonyl malonate ester **3g** 는 mono-와 diallylated product 의 혼합물을 생성하였지만, allyl alcohol **2a** 를 증량 (4 equiv)하고 DMADA 도 증량 (4 equiv)하였을 때 오로지 diallylated product **4ag** 만을 높은 수율로 생성해냈다 (Table 2, entry 6). 이런 DMADA/palladium 반응은 다른 알릴 알코올 기질 (i.e., **2b-2e**)에서도 적용 가능했으며 이들의 합성물들을 합성해냈다. 알킬기 치환된 1 차 알릴 알코올 **2b** 에서는 선형 알릴 물질 **4ba** 를 90% 수율로 얻어냈으며 이 화합물은 30:1 의 E/Z ratio 를 보였다 (Table 2, entry 7). 2 차 알릴 알코올 **2c** 는 single *trans* product **4ca** 를 85% 수율로 형성하였다 (Table 2, entry 8). cyclic secondary allylic alcohol **2d** 는 친핵체와 반응하여 높은 수율의 결과를 보여주었다 (Table 2, entry 9). 그러나 구조적으로 가려진 3 차 알릴 알코올 **2e** 에서는 반응이 진행되지 않았다 (Table 2, entry 10). 이것은 DMADA 의 trans-acetalization 이 잘 일어나지 않았기 때문인 것으로 보인다.

Table 2. 알릴 알코올과 탄소 친핵체들의 기질 범위 연구.<sup>a</sup>

Entry	Allylic alcohol <b>2</b>	Dicarbonyl compound <b>3</b>	Product <b>4</b>	<i>t</i> [h]	Yield [%] <sup>b</sup>
1	 <b>2a</b>	 <b>3b</b>	 <b>4ab</b>	1	94
2	<b>2a</b>	 <b>3c</b>	 <b>4ac</b>	1	99
3	<b>2a</b>	 <b>3d</b>	 <b>4ad</b>	1	84
4	<b>2a</b>	 <b>3e</b>	 <b>4ae</b>	20	98
5	<b>2a</b>	 <b>3f</b>	 <b>4af</b>	2	84
6 <sup>c</sup>	<b>2a</b>	 <b>3g</b>	 <b>4ag</b>	12	90
7	 <b>2b</b>	 <b>3a</b>	 <b>4ba</b> ( <i>E/Z</i> , 30:1)	3	90
8	 <b>2c</b>	<b>3a</b>	 <b>4ca</b>	20	85

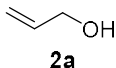
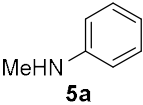
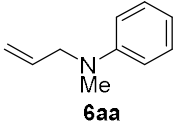
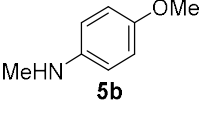
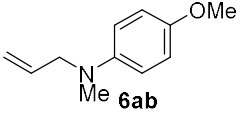

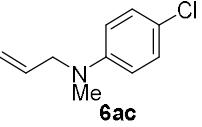
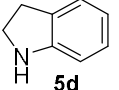
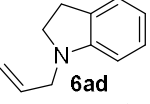
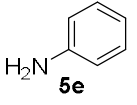
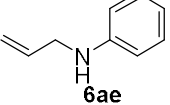


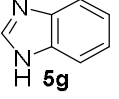
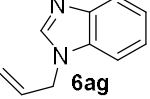

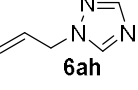
9		3a		3	96
10		3a		20	<1


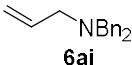
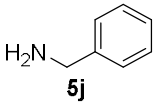
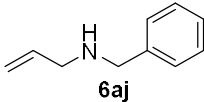
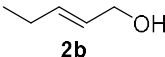
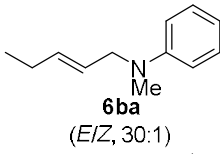
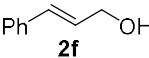
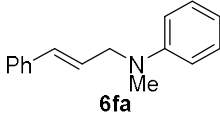
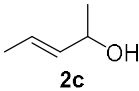
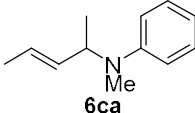
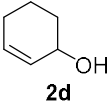
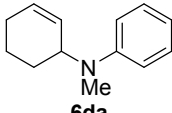
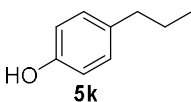
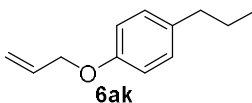
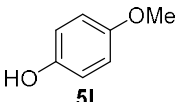
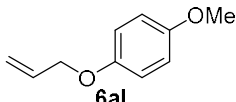
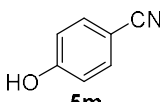
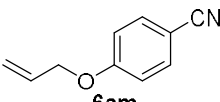
<sup>a</sup>Reaction conditions: **2** (2 mmol), **3** (1 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 mmol), DMADA (2 mmol), in MeCN (2 mL). <sup>b</sup>Isolated yield. <sup>c</sup>4 equiv. of **2a** and DMADA were employed.

중성적인 반응 조건 덕분에, 우리는 DMADA 를 활용한 direct allylation 을 질소 친핵체에서도 성공적으로 수행하였다.<sup>11</sup> 비록 MeCN 이 탄소 친핵체와의 반응에서 선호되었지만 THF 가 질소 친핵체에서의 반응에선 더 성공적이었기에 용매 THF 를 사용하여 실험을 진행하였다. 질소 친핵체를 allylic alcohol **2a** 에 적용시켰을 때 최적화된 조건 (i.e., 2 equiv of DMADA and 0.05 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub> in THF at 50 °C)을 찾았다. Table 3 에 소개된 것처럼, 전자가 풍부하거나 적은 2 차 aniline 을 allylation 하였을 때, 아주 높은 수율로 원하는 화합물을 얻을 수 있었다 (Table 3, entries 1-4). 하지만, 1 차 aniline 인 **5e** 를 친핵체로 적용하였을 때, 낮은 수득률 (28%)를 보였다 (Table 3, entry 5). 이것은 반응이 진행될 때 amidine 이 상당한 양 (64%)으로 생성되었기 때문이다.<sup>8,12</sup> 다양한 방향족 N-heterocycle 들도 적용되었는데, imidazole, benzimidazole, 1,2,4-triazole 을 친핵체로 사용했을 때 allylation 이 성공적으로 수행되어 높은 수율로 결과물을 얻을 수 있었다 (Table 3, entries 6-8). 2 차 아민인 dibenzylamine **5i** 도 도 역시 합성이 잘 진행되었다 (Table 3, entry 9). 하지만, 1 차 아민인 **5j** 는 좋은 기질이 아니었다 (Table 3, entry 10). N-methylaniline **5a** 와 다양한 알릴 알코올 **2b-2d**, **2f** 를 사용하여 추가적인 실험을 진행하였다. 탄소 친핵체와 유사하게 1 차 알릴 알코올 **2b** 와 **2f** 로 선형이자

*trans* 인 물질 **6ba** 와 **6fa** 를 우세한 생성물로 얻을 수 있었다 (Table 3, entries 11 and 12). allylic amination 이 환형과 비환형 2 차 아릴 알코올에서도 일어났지만 반응 시간이 길었다 (Table 3, entries 13 and 14). 이런 DMADA/palladium reaction 은 phenolic 산소 친핵체에서도 응용될 수 있었다.<sup>13</sup> allyl phenyl ether 들이 높은 수율로 얻어질 수 있었고, 전자가 풍부한 페놀 친핵체일 수록 반응이 잘 진행되었다 (Table 3, entries 15 and 16). 반면에, 전자가 부족한 페놀인 **5m** 은 친핵체로 좋지 않았다 (Table 3, entry 17).

Table 3. 알릴 알코올과 질소 및 산소 친핵체들의 기질 범위 연구.<sup>a</sup>

Entry	Allylic alcohol <b>2</b>	Heteroatom nucleophile <b>5</b>	Product <b>6</b>	<i>t</i> [h]	Yield [%] <sup>b</sup>
1	 <b>2a</b>	 <b>5a</b>	 <b>6aa</b>	4	93
2	<b>2a</b>	 <b>5b</b>	 <b>6ab</b>	2	95
3	<b>2a</b>	 <b>5c</b>	 <b>6ac</b>	20	98
4	<b>2a</b>	 <b>5d</b>	 <b>6ad</b>	20	88
5	<b>2a</b>	 <b>5e</b>	 <b>6ae</b>	20	28
6	<b>2a</b>	 <b>5f</b>	 <b>6af</b>	2	93
7	<b>2a</b>	 <b>5g</b>	 <b>6ag</b>	4	98
8	<b>2a</b>	 <b>5h</b>	 <b>6ah</b>	2	93

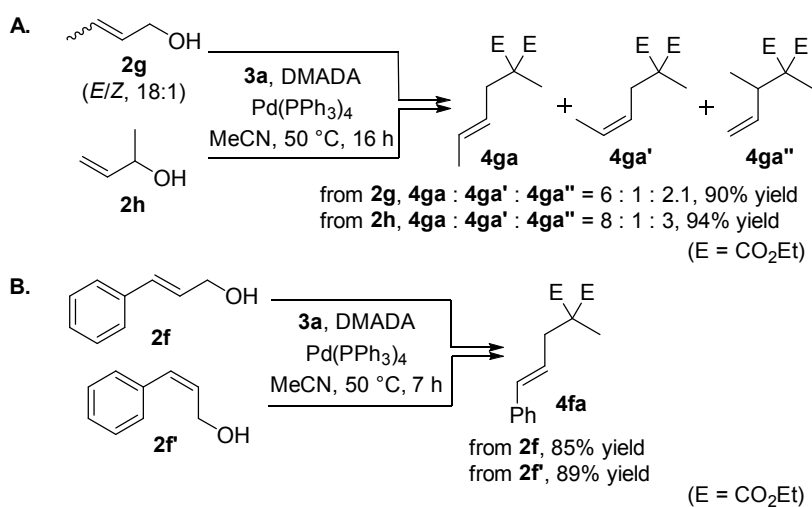
9	<b>2a</b>	 <b>5i</b>	 <b>6ai</b>	4	98
10	<b>2a</b>	 <b>5j</b>	 <b>6aj</b>	20	<1
11	 <b>2b</b>	<b>5a</b>	 <b>6ba</b> ( <i>E/Z</i> , 30:1)	2	94
12	 <b>2f</b>	<b>5a</b>	 <b>6fa</b>	1	90
13	 <b>2c</b>	<b>5a</b>	 <b>6ca</b>	20	65
14	 <b>2d</b>	<b>5a</b>	 <b>6da</b>	20	73
15	<b>2a</b>	 <b>5k</b>	 <b>6ak</b>	0.5	94
16	<b>2a</b>	 <b>5l</b>	 <b>6al</b>	2	98
17	<b>2a</b>	 <b>5m</b>	 <b>6am</b>	20	<1

<sup>a</sup>Reaction conditions: **2** (2 mmol), **5** (1 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 mmol), DMADA (2 mmol), in THF (2 mL). <sup>b</sup>Isolated yield.

이런 반응의 기전을 이해하기 위해, 우리는 isomeric allylic alcohol들을 이용한 실험을 진행하였다 (Scheme 2). 두개의 regioisomeric butyl alcohol인 **2g**<sup>14</sup>와 **2h**가 regioisomeric products **4ga**, **4ga'**, **4ga''**를 비슷한 비율로 생산하였다 (Scheme 2A). 이런 결과는 이전에 Norrby 그룹에서 isomeric allylic acetate를 사용했던 실험과

동등한 결과를 보인다.<sup>15</sup> 추가적으로 *trans*와 *cis* isomer의 cinnamyl alcohol (**2f** and **2f'**)를 적용하였을 때, 같은 물질인 **4fa**만이 *trans* 선택적으로 합성되었다 (Scheme 2B). 이런 결과와 Tsuji-Trost reaction 반응 기전을 미루어 볼 때, *syn-anti* isomerization이  $\eta^3 \pi$ -allyl complex에서 일어난다는 것을 알 수 있다.<sup>2,15</sup>

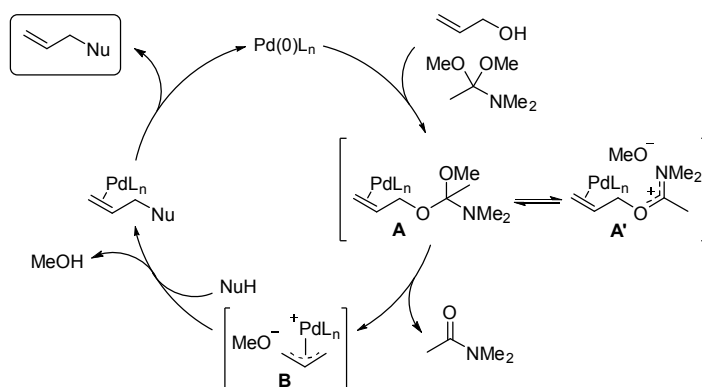
Scheme 2. Isomeric allylic alcohol들을 이용한 allylation 반응.



**2a**와 **3a**가 반응에 참여하는 것을 <sup>1</sup>H NMR 분석으로 모니터링 해보았을 때 우리는 DMA와 MeOH이 product인 **4aa**가 생성됨에 따라 증가하는 것을 볼 수 있었다.<sup>16,17</sup> 이 allylation 반응에서 allylic alcohol, DMADA, Palladium catalyst들은 반응속도론적으로 1차를 따랐다.<sup>17</sup> 하지만 반응속도에 친핵체 **3a**의 농도는 관련이 되지 않은 결과를 보였다. 이런 결과를 isomeric allylic alcohol 결과 (Scheme 2)와 적용하였을 때, 우리는 이 반응이 DMADA가 allylic alcohol을 직접적으로 활성화시키고  $\pi$ -allyl complex를 형성하면서 진행된다는 것을 예측할 수 있었다 (Scheme 3). 이들의 결합을 통해  $\eta^2 \pi$ -allyl complex **A**와 **A'**를 형성할 수 있다. 이 complex들은 평형상태로 존재하면서 oxidative addition을 통해  $\eta^3 \pi$ -

allyl complex **B**를 형성한다. **B**가 친핵체와 반응하여 알릴화된 물질을 형성한다. oxidative addition 과정에서 **A**의 amide acetal 부분과 **A'**의 aza-oxo-stabilized carbenium 부분이 이탈기로 작용하여 DMA와 methoxide를 방출한다. 방출된 methoxide ion은 염기성이 충분하여 soft pronucleophiles의 수소를 충분히 받아드리고, Tsuji-Trost reaction에서 allylic carbonate들과 유사하게 작용하여 추가적인 염기가 필요없다.<sup>18</sup>

Scheme 3. DMADA를 활용한 allylation 반응의 기전.



### III. Conclusions

요약하자면, Tsuji-Trost reaction 에서 우리는 DMADA 를 *in situ* activator 로 적용하여 알릴 알코올을 직접적으로 활성화하였다. 이런 allylation 반응은 간단한  $\text{Pd(PPh}_3)_4$  팔라듐 촉매를 사용하며 온화하고 중성적인 반응조건이 특징이다. 특별하게 고안된 리간드나, 산, 염기성 첨가물이 필요가 없다. 중성적인 조건에 의해 탄소 친핵체뿐만 아니라 질소 친핵체 그리고 산소 친핵체들도 적용가능하다. 향후 추가적인 연구를 통해 기질의 범위를 확장할 수 있고, chiral phosphine ligand 도입을 통해 비대칭 반응을 시도해볼 수 있다.

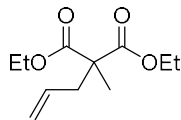


## IV. Experimental Section

**General Procedures:** 모든 화합물은 시약으로 구입하여 사용했다. 모든 실험은 질소 기류 하에서 수행하였고, 증류된 무수 용매로 진행하였다. 반응은 박층 크로마토그래피 (Merck®, silica gel 60 F<sub>254</sub>) 분석을 통해 확인하였다. <sup>1</sup>H NMR (nuclear magnetic resonance) spectra 는 400, 600, 800 MHz로 확인하였고, <sup>13</sup>C NMR spectra 는 75, 100, 150, 200 MHz로 확인하였다. chemical shift ( $\delta$ ) 는 ppm (parts per million) 단위로, coupling constant ( $J$ ) 는 Hz (herts) 로 나타내었고, 용매의 시그널은 internal reference를 통해 확인하였다 ( $\delta$ =7.24 ppm for CD<sub>3</sub>Cl,  $\delta$ =1.94 ppm for CD<sub>3</sub>CN, and  $\delta$ =0 for TMS). 시그널의 multiplicity는 다음과 같다: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. <sup>1</sup>H NMR spectroscopic data는 다음 순서를 따른다: chemical shift (multiplicity, coupling constant, integration). IR (infrared) spectra 는 푸리에 변환 infrared spectrometer로 측정하였다. High-resolution mass spectra (HRMS)는 fast atom bombardment (FAB) 또는 electron ionization (EI)를 이용하여 측정하였다. 이전에 보고된 화합물들의 구조는 문헌에 알려진 <sup>1</sup>H NMR와 <sup>13</sup>C NMR spectroscopic data와 비교하였다.

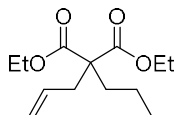
**General Procedure for the Allylation of Dicarboxyl Compounds with Allyl Alcohols:** **3** (1.0 mmol)이 MeCN (2mL)에 있는 용액에 **2** (2.0 mmol), dimethylacetamide dimethyl acetal (2.0 mmol),과 Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 mmol)을 상온에서 첨가한다. 혼합물은 50 °C에서 N<sub>2</sub> 기류하에 교반하였고, TLC 분석을 통해 **3**이 완전히 변화할 때까지 반응시킨다. 상온에서 반응 혼합액에 NH<sub>4</sub>Cl 포화수용액으로 반응을 종결하고 H<sub>2</sub>O로 희석한다. 혼합물은 EtOAc를 이용하여 추출한다. 추출된 유기층 용액은 MgSO<sub>4</sub>로 건조하고 감압농축한다. 얻어진 물질을 silica gel로 충전된 컬럼 크로마토그래피 (hexane/EtOAc)로 분리하여 원하는 화합물을 얻는다.

**Diethyl 2-allyl-2-methylmalonate (4aa)<sup>19</sup>**



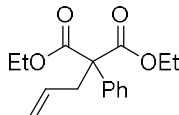
Colorless oil;  $R_f = 0.55$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.66 (tdd,  $J = 7.2, 9.9, 17.0$  Hz, 1H), 5.07 (d,  $J = 17.0$  Hz, 1H), 5.06 (d,  $J = 10.0$  Hz, 1H), 4.15 (q,  $J = 7.1$  Hz, 4H), 2.58 (d,  $J = 7.4$  Hz, 2H), 1.35 (s, 3H), 1.21 ppm (t,  $J = 7.1$  Hz, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 171.9 (2 C), 132.6, 119.0, 61.2 (2 C), 53.4, 40.0, 19.7, 14.0 ppm (2 C).

**Diethyl 2-allyl-2-propylmalonate (4ab)<sup>19</sup>**



Colorless oil;  $R_f = 0.36$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.62 (tdd,  $J = 7.3, 9.9, 17.1$  Hz, 1H), 5.06 (d,  $J = 17.2$  Hz, 1H), 5.04 (d,  $J = 9.9$  Hz, 1H), 4.15 (q,  $J = 7.1$  Hz, 4H), 2.61 (d,  $J = 7.4$  Hz, 2H), 1.84–1.78 (m, 2H), 1.21 (t,  $J = 7.1$  Hz, 6H), 1.26–1.13 (m, 2H), 0.89 ppm (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 171.3 (2 C), 132.6, 118.7, 61.0 (2 C), 57.4, 36.9, 34.4, 17.3, 14.4, 14.1 ppm (2 C).

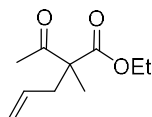
**Diethyl 2-allyl-2-phenylmalonate (4ac)<sup>20</sup>**



Colorless oil;  $R_f = 0.33$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.43–7.37 (m, 2H), 7.34–7.23 (m, 3H), 5.75 (tdd,  $J = 7.1, 10.1, 17.1$  Hz, 1H), 5.05 (d,  $J = 16.9$  Hz, 1H), 5.02 (d,  $J = 10.2$  Hz, 1H), 4.25–4.14 (m, 4H), 3.06 (d,  $J = 7.1$  Hz, 2H), 1.22 ppm

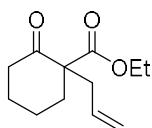
(t,  $J = 7.2$  Hz, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 170.2$  (2 C), 136.7, 133.0, 128.0 (2 C), 128.0 (2 C), 127.5, 118.7, 62.6, 61.5 (2 C), 40.2, 14.0 ppm (2 C).

**Ethyl 2-acetyl-2-methylpent-4-enoate (4ad)<sup>21</sup>**



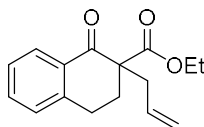
Colorless oil;  $R_f = 0.37$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.59$  (tdd,  $J = 7.3, 9.9, 17.1$  Hz, 1H), 5.06–5.01 (m, 2H), 4.14 (q,  $J = 7.1$  Hz, 2H), 2.58 (dd,  $J = 6.9, 14.2$  Hz, 1H), 2.44 (dd,  $J = 7.6, 14.0$  Hz, 1H), 2.09 (s, 3H), 1.27 (s, 3H), 1.21 ppm (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 204.9, 172.4, 132.6, 118.9, 61.3, 59.3, 39.2, 26.1, 18.8, 14.0$  ppm.

**Ethyl 1-allyl-2-oxocyclohexane-1-carboxylate (4ae)<sup>22</sup>**



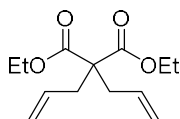
Colorless oil;  $R_f = 0.32$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.71$  (tdd,  $J = 7.6, 9.7, 17.4$  Hz, 1H), 5.01 (d,  $J = 13.6$  Hz, 2H), 4.15 (q,  $J = 7.2$  Hz, 2H), 2.58 (dd,  $J = 7.0, 14.0$  Hz, 1H), 2.49–2.37 (m, 3H), 2.30 (dd,  $J = 7.8, 13.9$  Hz, 1H), 2.03–1.93 (m, 1H), 1.78–1.53 (m, 3H), 1.48–1.37 (m, 1H), 1.22 ppm (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 207.5, 171.5, 133.3, 118.2, 61.2, 60.9, 41.1, 39.3, 35.8, 27.5, 22.5, 14.2$  ppm.

**Ethyl 2-allyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4af)<sup>23</sup>**



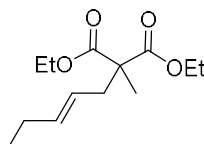
Yellow oil;  $R_f = 0.38$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.01 (d,  $J$  = 7.9 Hz, 1H), 7.42 (t,  $J$  = 7.5 Hz, 1H), 7.26 (t,  $J$  = 7.7 Hz, 1H), 7.17 (d,  $J$  = 7.7 Hz, 1H), 5.80 (tdd,  $J$  = 7.3, 10.0, 17.2 Hz, 1H), 5.10 (d,  $J$  = 18.1 Hz, 1H), 5.06 (d,  $J$  = 10.3 Hz, 1H), 4.10 (dq,  $J$  = 1.7, 7.1 Hz, 2H), 3.09–2.98 (m, 1H), 2.88 (td,  $J$  = 4.9, 17.4 Hz, 1H), 2.68 (ddd,  $J$  = 7.4, 14.0, 24.5 Hz, 2H), 2.49 (td,  $J$  = 4.9, 13.8 Hz, 1H), 2.15–2.05 (m, 1H), 1.12 ppm (t,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 194.9, 171.3, 143.0, 133.3 (2 C), 131.9, 128.6, 127.8, 126.6, 118.7, 61.2, 57.1, 38.5, 30.4, 25.7, 14.0 ppm.

**Diethyl 2,2-diallylmalonate (4ag)<sup>20</sup>**



Colorless oil;  $R_f = 0.30$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.63 (tdd,  $J$  = 7.1, 10.0, 17.0 Hz, 2H), 5.08 (d,  $J$  = 16.7 Hz, 2H), 5.07 (d,  $J$  = 10.5 Hz, 2H), 4.15 (q,  $J$  = 7.1 Hz, 4H), 2.61 (d,  $J$  = 7.3 Hz, 4H), 1.22 ppm (t,  $J$  = 7.1 Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 170.8 (2 C), 132.3 (2 C), 119.1 (2 C), 61.2 (2 C), 57.2, 36.7 (2 C), 14.1 ppm (2 C).

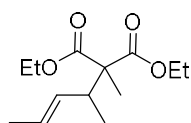
**Diethyl (E)-2-methyl-2-(pent-2-en-1-yl)malonate (4ba)**



Colorless oil;  $R_f = 0.43$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 5.56–5.46 (m, 1H), 5.25 (td,  $J$  = 7.5 Hz, 15.0 Hz, 1H), 4.14 (q,  $J$  = 7.0 Hz, 4H), 2.51 (d,  $J$  = 7.6

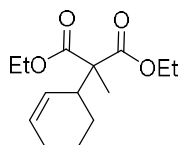
Hz, 2H), 1.96 (quintet,  $J = 7.1, 14.4$  Hz, 2H), 1.33 (s, 3H), 1.21 (t,  $J = 7.1$  Hz, 6H), 0.91 ppm (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 172.0$  (2 C), 136.9, 122.7, 61.2, 61.1, 53.7, 38.8, 25.6, 19.7, 14.1 (2 C), 13.7 ppm; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 2983, 1731, 1461, 1378, 1238, 1193, 1108, 1023, 971, 862\text{ cm}^{-1}$ ; HRMS (FAB):  $m/z$ : calcd. for  $\text{C}_{13}\text{H}_{23}\text{O}_4$ : 243.1596  $[\text{M}+\text{H}]^+$ ; found: 243.1593.

**Diethyl (*E*)-2-methyl-2-(pent-3-en-2-yl)malonate (4ca)**



Yellow oil;  $R_f = 0.27$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.46$  (qd,  $J = 6.43, 15.1$  Hz, 1H), 5.30–5.36 (m, 1H), 4.19–4.08 (m, 4H), 2.91 (quintet,  $J = 7.3, 14.7$  Hz, 1H), 1.62–1.58 (m, 3H), 1.30 (s, 3H), 1.21 (q,  $J = 6.88$  Hz, 6H), 1.01 ppm (d,  $J = 6.84$  Hz, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.6, 171.6, 131.5, 126.8, 61.0$  (2 C), 57.5, 41.4, 17.9, 16.6, 16.2, 14.1, 14.0 ppm; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 2983, 1734, 1458, 1380, 1245, 1100, 1028, 970, 862\text{ cm}^{-1}$ ; HRMS (FAB):  $m/z$ : calcd. for  $\text{C}_{13}\text{H}_{23}\text{O}_4$ : 243.1596  $[\text{M}+\text{H}]^+$ ; found: 243.1604.

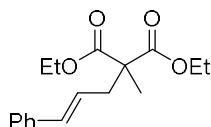
**Diethyl 2-(cyclohex-2-en-1-yl)-2-methylmalonate (4da)**



Colorless oil;  $R_f = 0.42$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 5.70$ –5.78 (m, 1H), 5.49 (td,  $J = 1.6, 10.2$  Hz, 1H), 4.22–4.08 (m, 4H), 3.06–2.96 (m, 1H), 1.99–1.89 (m, 2H), 1.80–1.71 (m, 1H), 1.67–1.57 (m, 1H), 1.57–1.47 (m, 1H), 1.29 (s, 4H), 1.21 ppm (td,  $J = 1.3, 7.1$  Hz, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 171.6, 171.5, 129.3, 127.6, 61.1$  (2 C), 56.8, 40.0, 24.9, 24.3, 22.2, 16.1, 14.0 ppm (2 C); IR ( $\text{CHCl}_3$ ):

$\nu_{\max}$  = 2936, 1730, 1248, 1224, 1104, 1022, 862  $\text{cm}^{-1}$ ; HRMS (EI):  $m/z$ : calcd. for  $\text{C}_{14}\text{H}_{23}\text{O}_4$ : 255.1591  $[\text{M}+\text{H}]^+$ ; found: 255.1591.

**Diethyl 2-cinnamyl-2-methylmalonate (4fa)**<sup>24</sup>

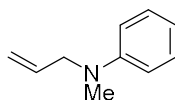


Colorless oil;  $R_f$  = 0.38 (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.23–7.32 (m, 4H), 7.21–7.16 (m, 1H), 6.43 (d,  $J$  = 15.7 Hz, 1H), 6.09 (td,  $J$  = 7.7, 15.5 Hz, 1H), 4.11–4.24 (m, 4H), 2.75 (d,  $J$  = 7.5, 2H), 1.42 (s, 3H), 1.23 ppm (t,  $J$  = 7.1 Hz, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 171.8 (2 C), 137.0, 133.9, 128.4 (2 C), 127.3, 126.1 (2 C), 124.2, 61.2 (2 C), 53.8, 39.3, 19.9, 14.1 ppm (2 C).

**General Procedure for the Allylation of Nitrogen Nucleophiles with Allyl Alcohols:**

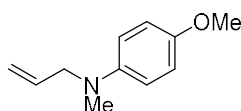
**5** (1.0 mmol)이 THF (2mL)에 있는 용액에 **2** (2.0 mmol), dimethylacetamide dimethyl acetal (2.0 mmol),과  $\text{Pd}(\text{PPh}_3)_4$  (0.05 mmol)을 상온에서 첨가한다. 혼합물은 50  $^\circ\text{C}$ 에서 질소 기류하에 교반하였고, TLC 분석을 통해 **5**이 완전히 변화할 때까지 반응시킨다. 상온에서 반응 혼합액에  $\text{NaHCO}_3$  포화수용액으로 반응을 종결하고  $\text{H}_2\text{O}$ 로 희석한다. 혼합물은 EtOAc를 이용하여 추출한다. 추출된 유기층 용액은  $\text{MgSO}_4$ 로 건조하고 감압농축한다. 얻어진 물질을 silica gel로 충전된 컬럼 크로마토그래피 (hexane/EtOAc 또는  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ )로 분리하여 원하는 화합물을 얻는다.

***N*-Allyl-*N*-methylaniline (6aa)**<sup>25</sup>



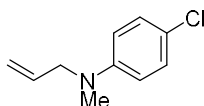
Yellow oil;  $R_f = 0.48$  (hexane/EtOAc=5:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.27\text{--}7.20$  (m, 2H), 6.72 (dd,  $J = 7.7, 14.4$  Hz, 3H), 5.91–5.80 (m, 1H), 5.22–5.12 (m, 2H), 3.92 (d,  $J = 5.0$  Hz, 2H), 2.94 ppm (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 149.5, 133.8, 129.1$  (2 C), 116.4, 116.1, 112.4 (2 C), 55.2, 38.0 ppm.

***N*-Allyl-4-methoxy-*N*-methylaniline (6ab)<sup>25</sup>**



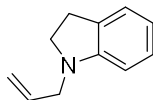
Colorless oil;  $R_f = 0.57$  (hexane/EtOAc=5:1);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.84$  (d,  $J = 9.2$  Hz, 2H), 6.74 (td,  $J = 9.2$  Hz, 2H), 5.86 (qd,  $J = 5.3, 10.9$  Hz, 1H), 5.19 (d,  $J = 17.0$  Hz, 1H), 5.16 (d,  $J = 10.5$  Hz, 1H), 3.84 (d,  $J = 5.5$  Hz, 2H), 3.76 (s, 3H), 2.87 ppm (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta = 151.7, 144.5, 134.3, 116.3, 114.7$  (2 C), 114.6 (2 C), 56.5, 55.7, 38.6 ppm.

***N*-Allyl-4-chloro-*N*-methylaniline (6ac)**



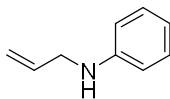
Colorless oil;  $R_f = 0.63$  (hexane/EtOAc=10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.24$  (d,  $J = 8.8$  Hz, 2H), 6.92–7.03 (m, 2H), 5.88 (ddd,  $J = 5.6, 10.7, 22.4$  Hz, 1H), 5.24 (d,  $J = 10.6$  Hz, 1H), 5.20 (d,  $J = 17.6$  Hz, 1H), 3.89 (d,  $J = 5.7$  Hz, 2H), 2.97 ppm (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 148.0, 133.2, 128.8$  (2 C), 121.1, 116.3, 113.5 (2 C), 55.3, 38.2 ppm; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 3406, 2889, 2463, 1597, 1499, 1371, 1246, 1208, 809$   $\text{cm}^{-1}$ ; HRMS (EI):  $m/z$ : calcd. for  $\text{C}_{10}\text{H}_{13}\text{ClN}$ : 182.0731  $[\text{M}+\text{H}]^+$ ; found: 182.0725.

**1-Allylindoline (6ad)**<sup>26</sup>



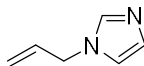
Yellow oil;  $R_f = 0.83$  (hexane/EtOAc=1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.06$  (q,  $J = 6.6$  Hz, 2H),  $6.66$  (t,  $J = 7.3$  Hz, 1H),  $6.51$  (d,  $J = 7.8$  Hz, 1H),  $5.92$  (tdd,  $J = 6.2, 10.5, 16.8$  Hz, 1H),  $5.29$  (dd,  $J = 1.6, 17.2$  Hz, 1H),  $5.19$  (dd,  $J = 1.4, 10.1$  Hz, 1H),  $3.71$  (d,  $J = 6.0$  Hz, 2H),  $3.34$  (t,  $J = 8.3$  Hz, 2H),  $2.96$  ppm (t,  $J = 8.3$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 152.1, 134.2, 130.2, 127.2, 124.4, 117.6, 117.2, 107.3, 53.2, 52.1, 28.5$  ppm.

**N-Allylaniline (6ae)**<sup>27</sup>



Colorless oil;  $R_f = 0.35$  (hexane/EtOAc= 10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.20$ – $7.13$  (m, 2H),  $6.71$  (t,  $J = 7.3$  Hz, 1H),  $6.64$  (d,  $J = 7.7$  Hz, 1H),  $5.91$  (ddd,  $J = 5.3, 10.4, 22.4$  Hz, 1H),  $5.28$  (qd,  $J = 1.6, 17.2$  Hz, 1H),  $5.16$  (qd,  $J = 1.4, 10.2$  Hz, 1H),  $4.05$  (br s, 1H),  $3.80$ – $3.73$  ppm (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 147.7, 135.2, 129.2$  (2 C),  $117.7, 116.4, 113.2$  (2 C),  $46.7$  ppm.

**1-Allyl-1H-imidazole (6af)**<sup>4e</sup>

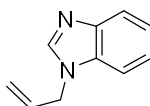


Yellow oil;  $R_f = 0.82$  (EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.42$  (s, 1H),  $7.01$  (s, 1H),  $6.85$  (s, 1H),  $5.90$  (tdd,  $J = 5.9, 10.7, 16.7$  Hz, 1H),  $5.22$  (d,  $J = 10.1$  Hz, 1H),  $5.12$  (d,  $J = 17.2$  Hz, 1H),  $4.49$  ppm (d,  $J = 5.1$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 137.0$ ,



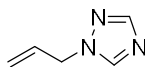
132.6, 129.2, 119.0, 118.6, 49.4 ppm.

**Allyl-1H-benzo[d]imidazole (6ag)<sup>4e</sup>**



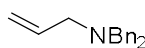
Yellow oil;  $R_f$  = 0.43 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}$ =100:10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.89 (s, 1H), 7.86–7.84 (m, 1H), 7.40–7.33 (m, 1H), 7.31–7.24 (m, 2H), 6.00 (tdd,  $J$  = 5.6, 10.9, 16.6 Hz, 1H), 5.28 (d,  $J$  = 10.2 Hz, 1H), 5.18 (d,  $J$  = 17.2 Hz, 1H), 4.72 ppm (d,  $J$  = 5.5 Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 143.6, 142.7, 133.6, 131.7, 122.8, 122.0, 120.1, 118.4, 109.8, 47.2 ppm.

**1-Allyl-1H-1,2,4-triazole (6ah)<sup>4e</sup>**



Colorless oil;  $R_f$  = 0.44 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ =10:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.05 (s, 1H), 7.93 (s, 1H), 6.05–5.93 (m, 1H), 5.33 (d,  $J$  = 10.0 Hz, 1H), 5.26 (d,  $J$  = 16.6 Hz, 1H), 4.77 ppm (d,  $J$  = 6.0 Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 152.0, 142.8, 131.1, 119.9, 52.1 ppm.

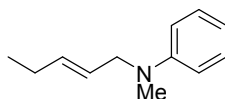
***N,N*-Dibenzylprop-2-en-1-amine (6ai)<sup>26</sup>**



Colorless oil;  $R_f$  = 0.83 (hexane/EtOAc=1:1);  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.39 (d,  $J$  = 7.8 Hz, 4H), 7.32 (t,  $J$  = 7.6, 4H), 7.24 (t,  $J$  = 6.9 Hz, 2H), 5.93 (tdd,  $J$  = 6.4, 10.4, 16.9 Hz, 1H), 5.22 (d,  $J$  = 17.3 Hz, 1H), 5.16 (d,  $J$  = 10.1 Hz, 1H), 3.59 (s, 4H), 3.08 ppm (d,  $J$  = 6.4 Hz, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 139.6 (2 C), 135.9, 128.7 (4 C), 128.1

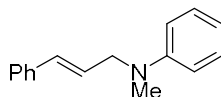
(4 C), 126.8 (2 C), 117.3, 57.7 (2 C), 56.3 ppm.

**(*E*)-*N*-Methyl-*N*-(pent-2-en-1-yl)aniline (6ba)**



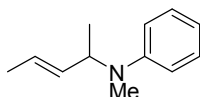
Yellow oil;  $R_f = 0.32$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.22–7.29 (m, 2H), 6.77 (d,  $J = 8.1$  Hz, 2H), 6.73 (t,  $J = 7.3$  Hz, 1H), 5.63–5.73 (m, 1H), 5.44–5.53 (m, 1H), 3.89 (dd,  $J = 0.8, 5.5$  Hz, 2H), 2.93 (s, 3H), 2.08 (quintet,  $J = 7.1, 14.1$  Hz, 2H), 1.01 ppm (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 149.6, 134.5, 129.0 (2 C), 124.0, 116.2, 112.5 (2 C), 54.5, 37.6, 25.3, 13.6 ppm; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 2965, 1600, 1506, 1371, 1204, 968, 747, 691$   $\text{cm}^{-1}$ ; HRMS (EI):  $m/z$ : calcd. for  $\text{C}_{12}\text{H}_{18}\text{N}$ : 176.1434  $[\text{M}+\text{H}]^+$ ; found: 176.1426.

***N*-Cinnamyl-*N*-methylaniline (6fa)<sup>28</sup>**



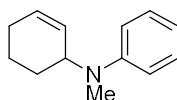
Colorless oil;  $R_f = 0.35$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.38–7.33 (m, 2H), 7.33–7.19 (m, 5H), 6.79 (d,  $J = 8.4$  Hz, 2H), 6.73 (t,  $J = 7.3$  Hz, 1H), 6.53 (d,  $J = 15.9$  Hz, 1H), 6.25 (td,  $J = 5.5, 15.8$  Hz, 1H), 4.09 (d,  $J = 5.4$  Hz, 2H), 2.98 ppm (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 149.5, 136.8, 131.2 (2 C), 129.1 (2 C), 128.5 (2 C), 127.3, 126.3, 125.7, 116.8, 112.6 (2 C), 54.9, 38.0 ppm.

**(*E*)-*N*-Methyl-*N*-(pent-3-en-2-yl)aniline (6ca)**



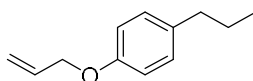
Yellow oil;  $R_f = 0.28$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 800 MHz):  $\delta = 7.26\text{--}7.21$  (m, 2H), 6.81 (d,  $J = 8$  Hz, 2H), 6.73–6.69 (m, 1H), 5.62–5.57 (m, 2H), 4.48–4.43 (m, 1H), 2.73 (s, 3H), 1.72 (td,  $J = 1.3, 6.0$  Hz, 3H), 1.24 ppm (d,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 150.0, 132.2, 129.0$  (2 C), 125.7, 116.4, 113.2 (2 C), 54.4, 31.2, 17.8, 16.2 ppm; IR ( $\text{CHCl}_3$ ):  $\nu_{\text{max}} = 2972, 2936, 1598, 1503, 1375, 1308, 1209, 1118, 970, 747, 691\text{ cm}^{-1}$ ; HRMS (EI):  $m/z$ : calcd. for  $\text{C}_{12}\text{H}_{18}\text{N}$ : 176.1434  $[\text{M}+\text{H}]^+$ ; found 176.1427.

***N*-(Cyclohex-2-en-1-yl)-*N*-methylaniline (6da)<sup>29</sup>**



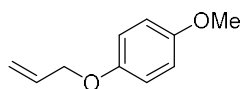
Yellow oil;  $R_f = 0.26$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (800 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.27\text{--}7.17$  (m, 2H), 6.78 (d,  $J = 8.3$  Hz, 2H), 6.68 (t,  $J = 7.2$  Hz, 1H), 5.94–5.86 (m, 1H), 5.61 (d,  $J = 10.1$  Hz, 1H), 4.43–4.39 (m, 1H), 2.77 (s, 3H), 2.10–1.98 (m, 2H), 1.89–1.75 (m, 2H), 1.70–1.52 ppm (m, 2H);  $^{13}\text{C}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 149.7, 130.6, 129.9, 129.1$  (2 C), 116.2, 112.8 (2 C), 54.9, 32.4, 25.3, 24.9, 21.5 ppm.

**1-(Allyloxy)-4-propylbenzene (6ak)<sup>30</sup>**



Yellow oil;  $R_f = 0.39$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.07$  (d,  $J = 8.5$  Hz, 2H), 6.83 (d,  $J = 8.6$  Hz, 2H), 6.11–5.99 (m, 1H), 5.50 (dd,  $J = 1.6, 17.3$  Hz, 1H), 5.26 (dd,  $J = 1.3, 10.5$  Hz, 1H), 4.50 (d,  $J = 5.2$  Hz, 2H), 2.51 (t,  $J = 7.6$  Hz, 2H), 1.65–1.55 (m, 2H), 0.92 ppm (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta = 156.6, 135.0, 133.5, 129.2$  (2 C), 117.5, 114.4 (2 C), 68.9, 37.2, 24.8, 13.8 ppm.

**1-(Allyloxy)-4-methoxybenzene (6al)**<sup>21,31</sup>



Colorless oil;  $R_f = 0.43$  (hexane/EtOAc=20:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.88–6.78 (m, 4H), 6.10–5.98 (m, 1H), 5.39 (dd,  $J = 1.5, 17.2$  Hz, 1H), 5.26 (dd,  $J = 1.3, 10.4$  Hz, 1H), 4.48 (d,  $J = 5.4$  Hz, 2H), 3.75 ppm (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 153.8, 152.7, 133.5, 117.4, 115.6 (2 C), 114.5 (2 C), 69.4, 55.6 ppm.

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## **VI. Supporting Information**

**VI-I. Spectrum Data**

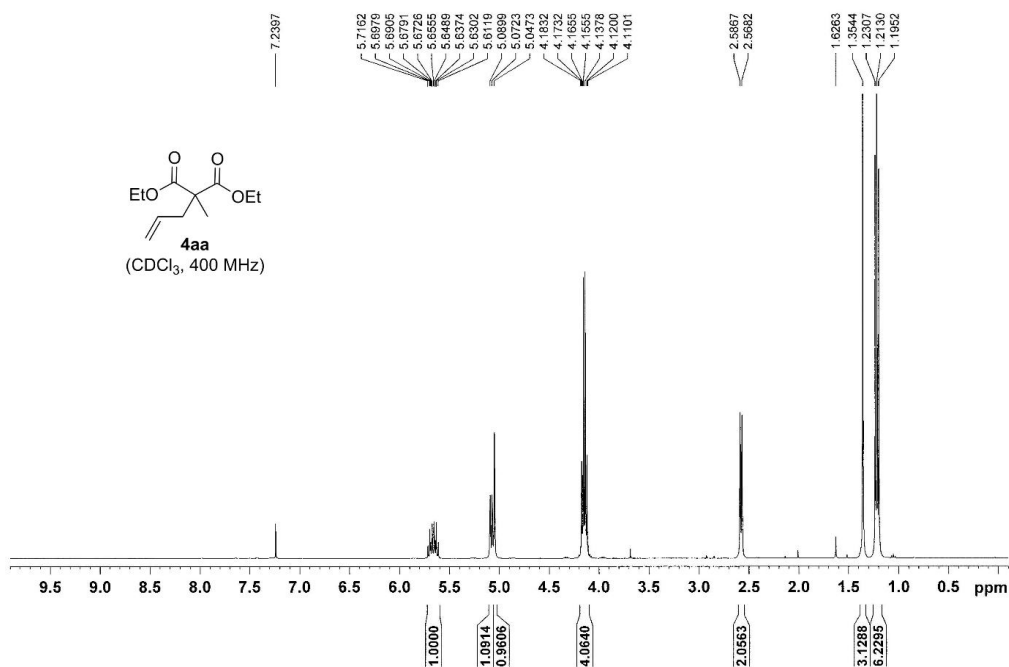
**VI-II. Allylation of 3a with the isomeric allylic alcohols**

**VI-III.  $^1\text{H}$  NMR Spectroscopy Study**

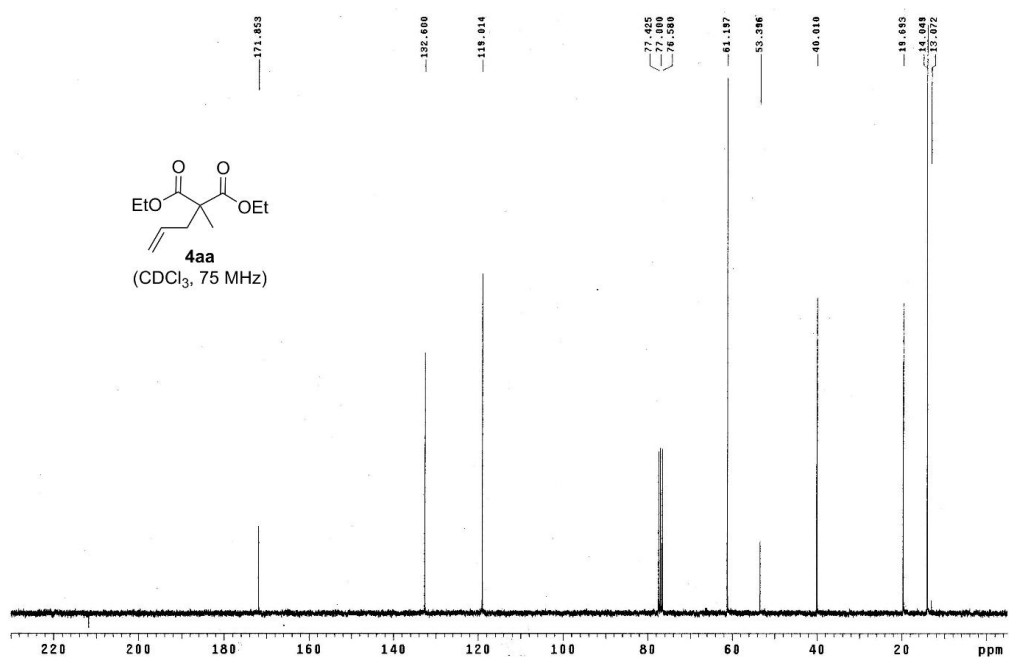
**VI-IV. Kinetic Experiment**

## VI-I. Spectrum Data

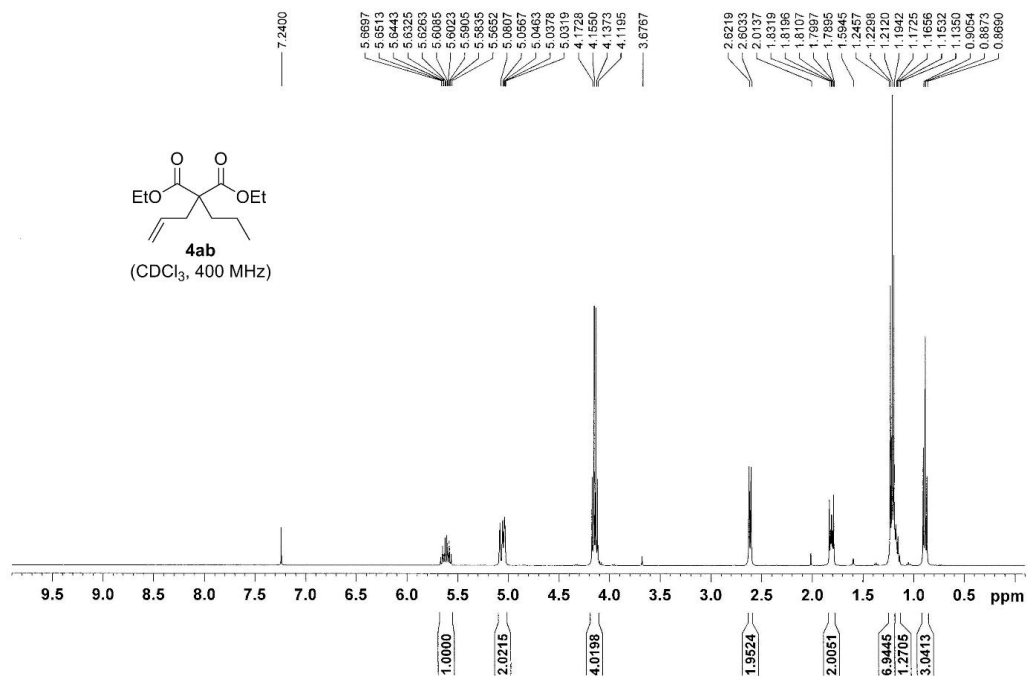
<sup>1</sup>H-NMR of **4aa**



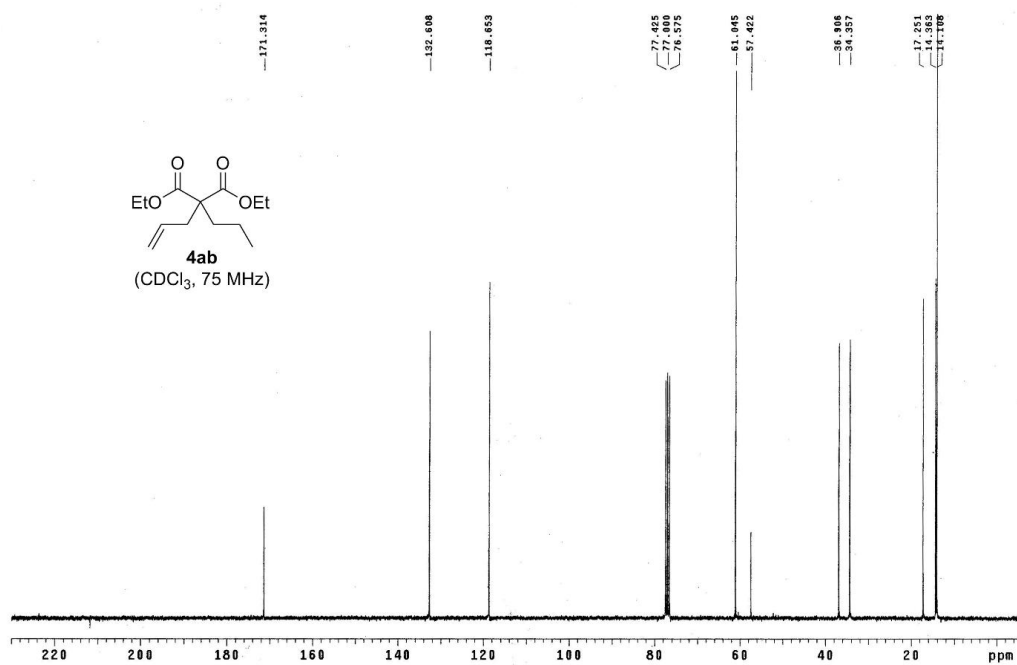
<sup>13</sup>C-NMR of **4aa**



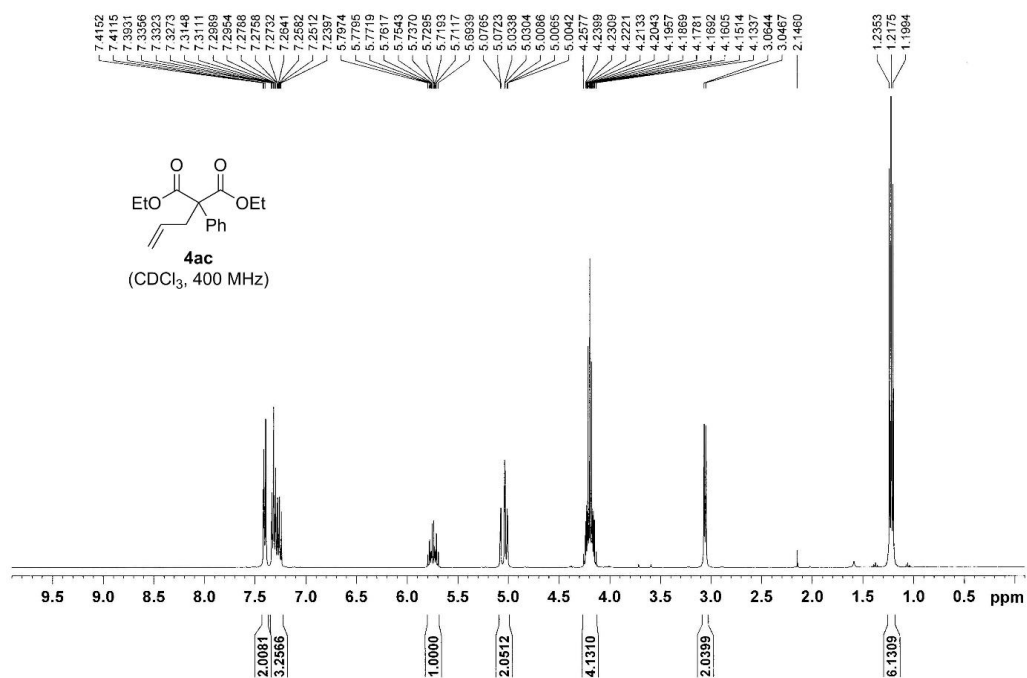
# <sup>1</sup>H-NMR of **4ab**



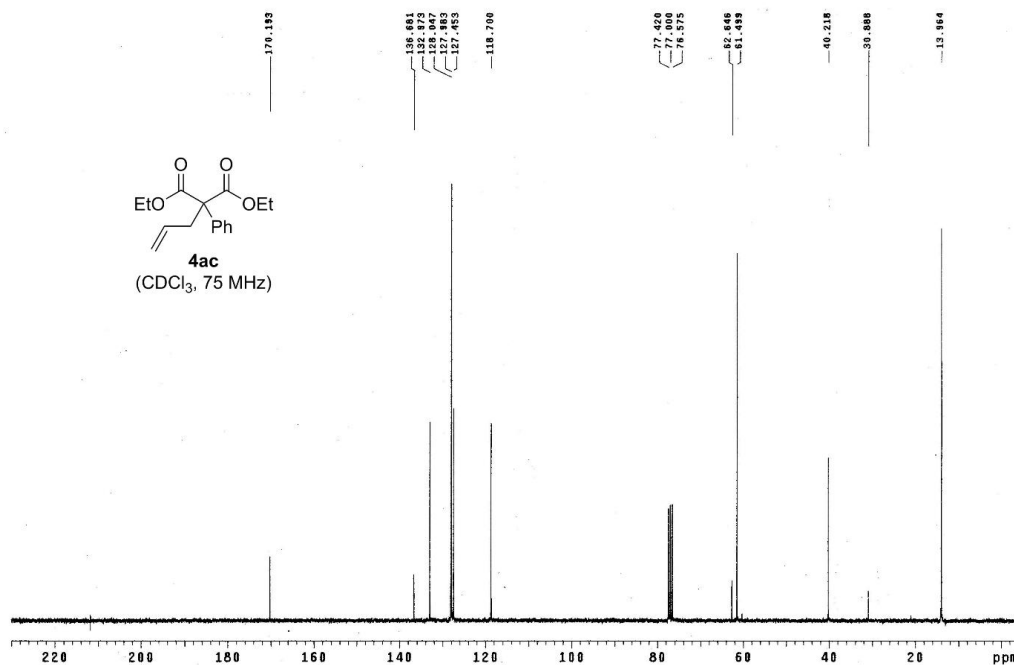
# <sup>13</sup>C-NMR of **4ab**



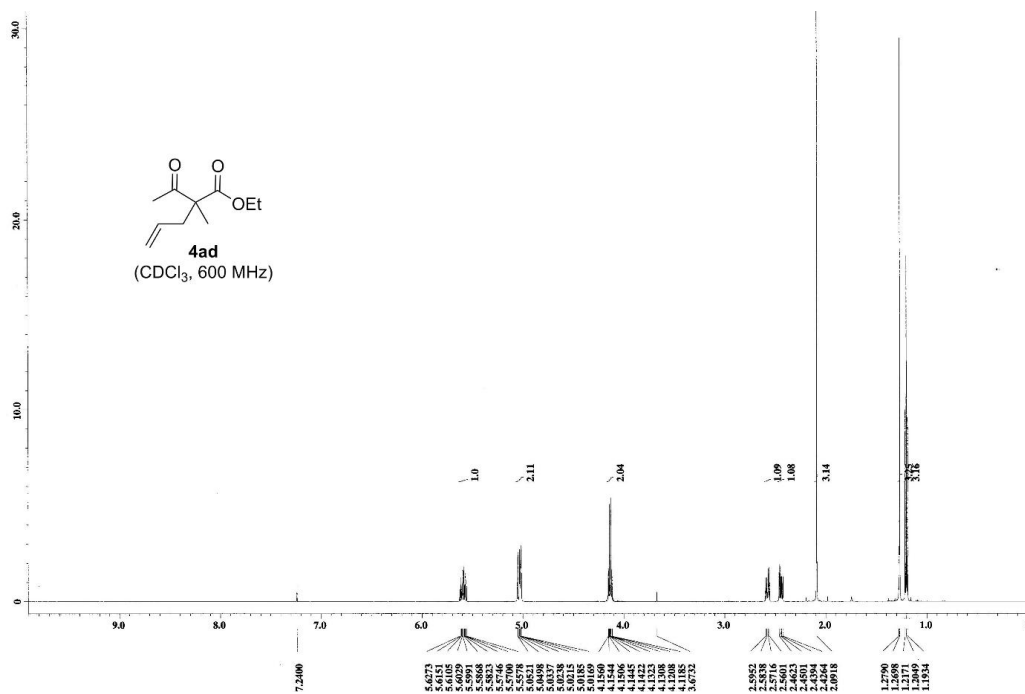
### <sup>1</sup>H-NMR of **4ac**



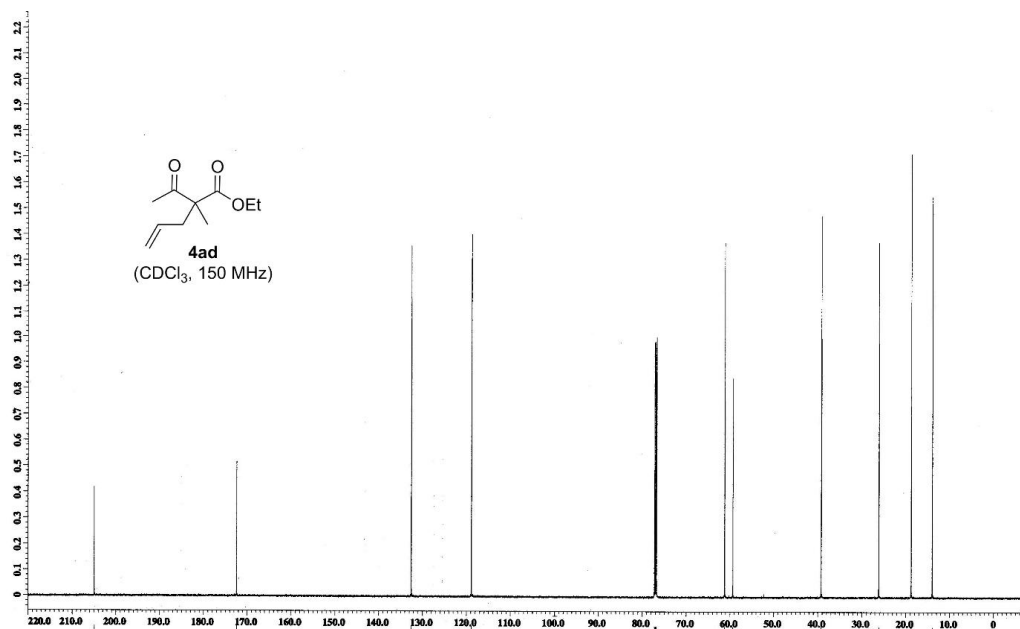
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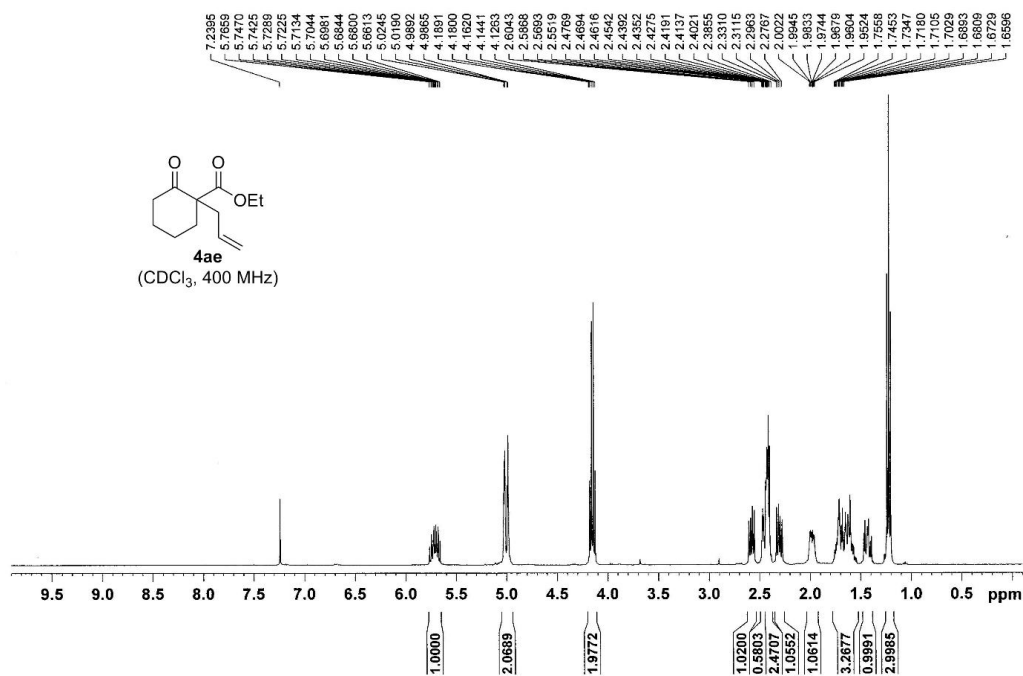
# <sup>1</sup>H-NMR of **4ad**



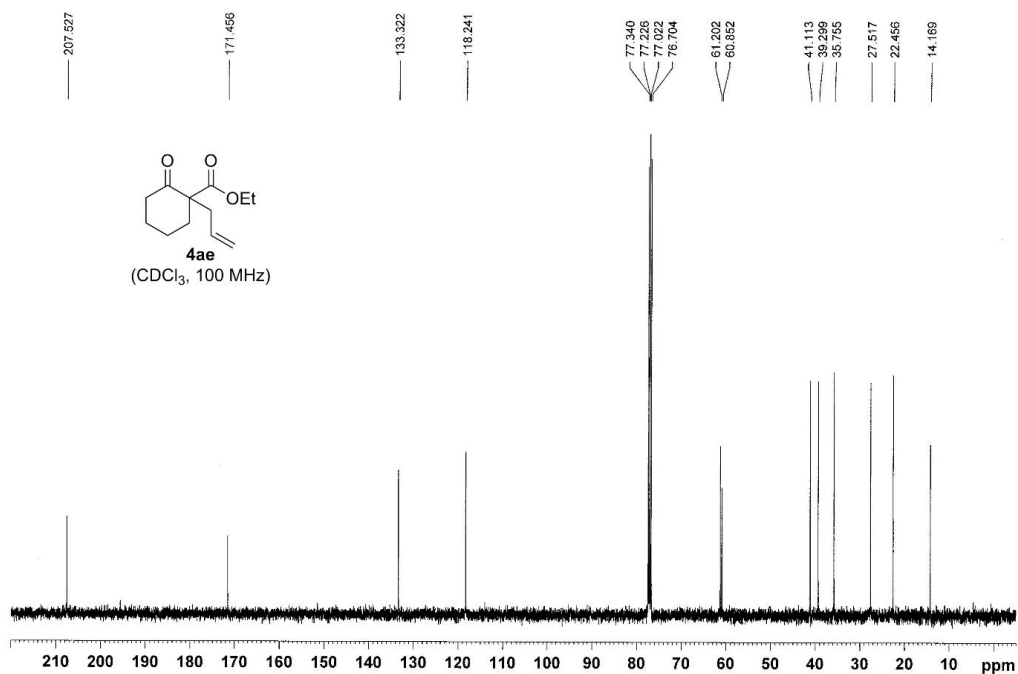
# <sup>13</sup>C-NMR of **4ad**



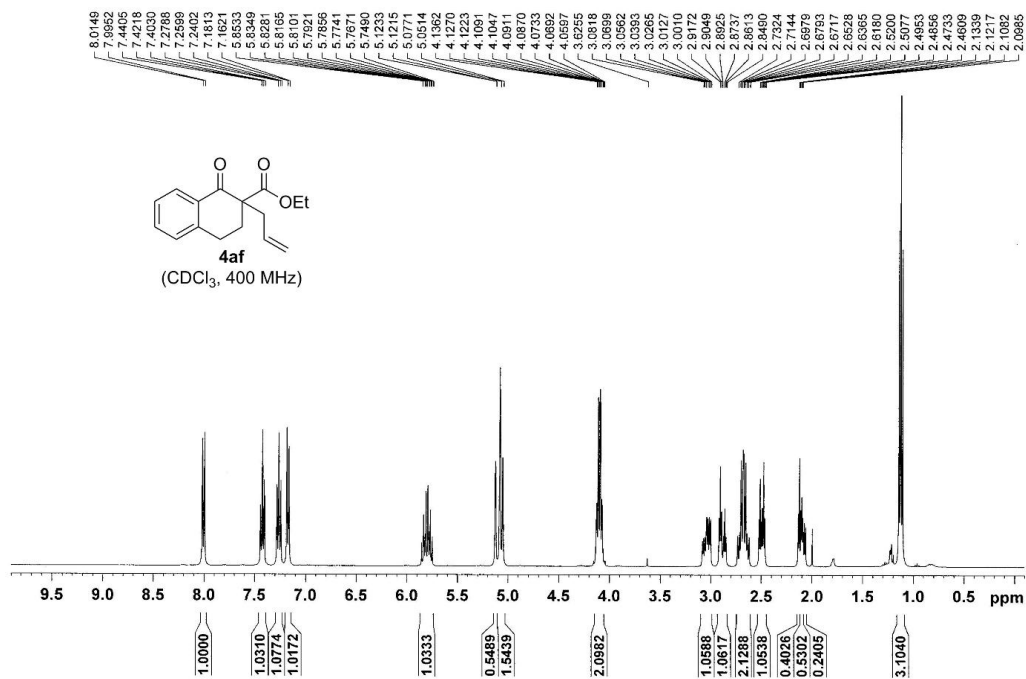
# <sup>1</sup>H-NMR of 4ae



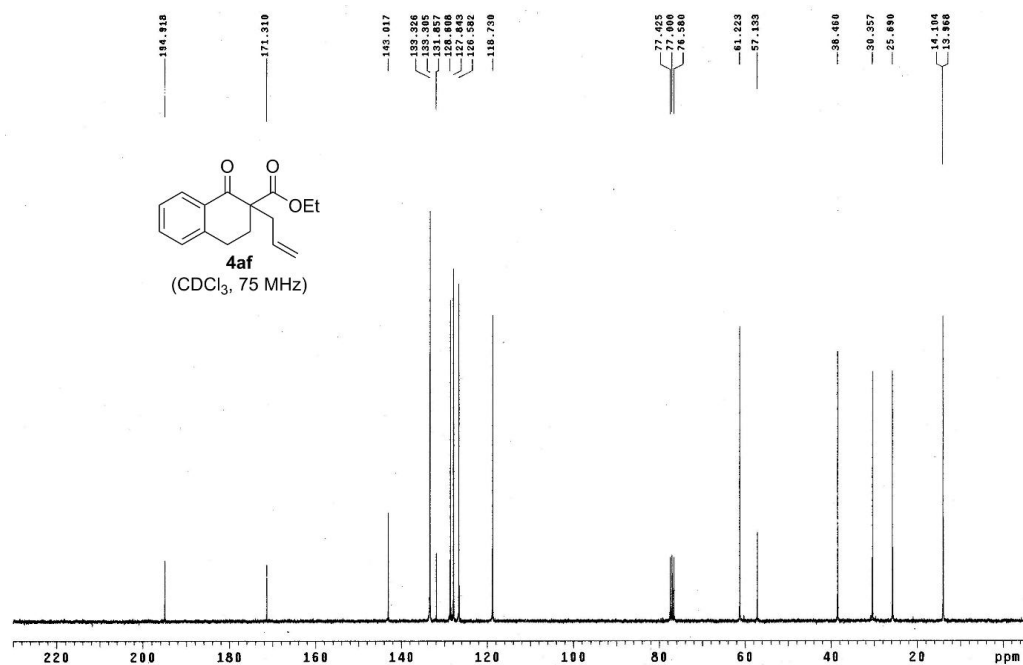
# <sup>13</sup>C-NMR of 4ae



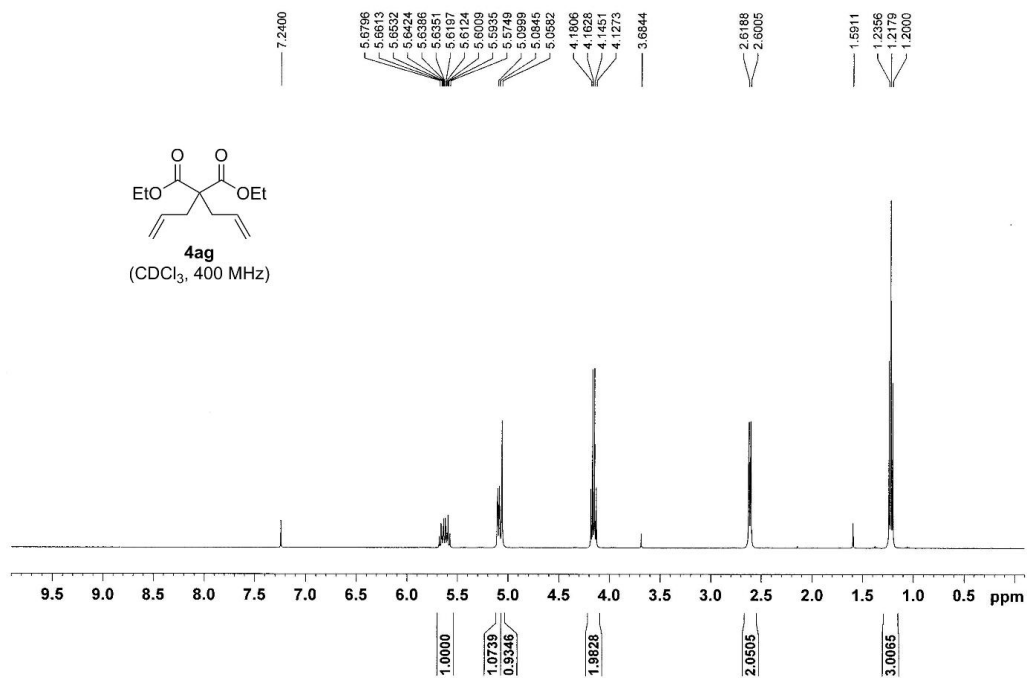
### <sup>1</sup>H-NMR of 4af



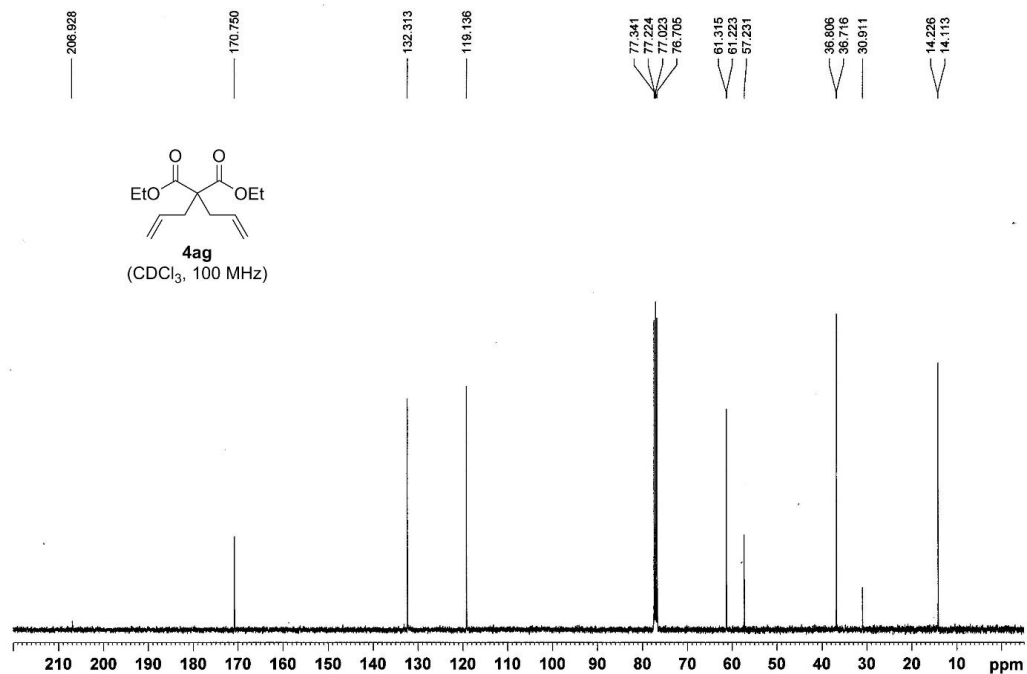
### <sup>13</sup>C-NMR of 4af



# <sup>1</sup>H-NMR of **4ag**

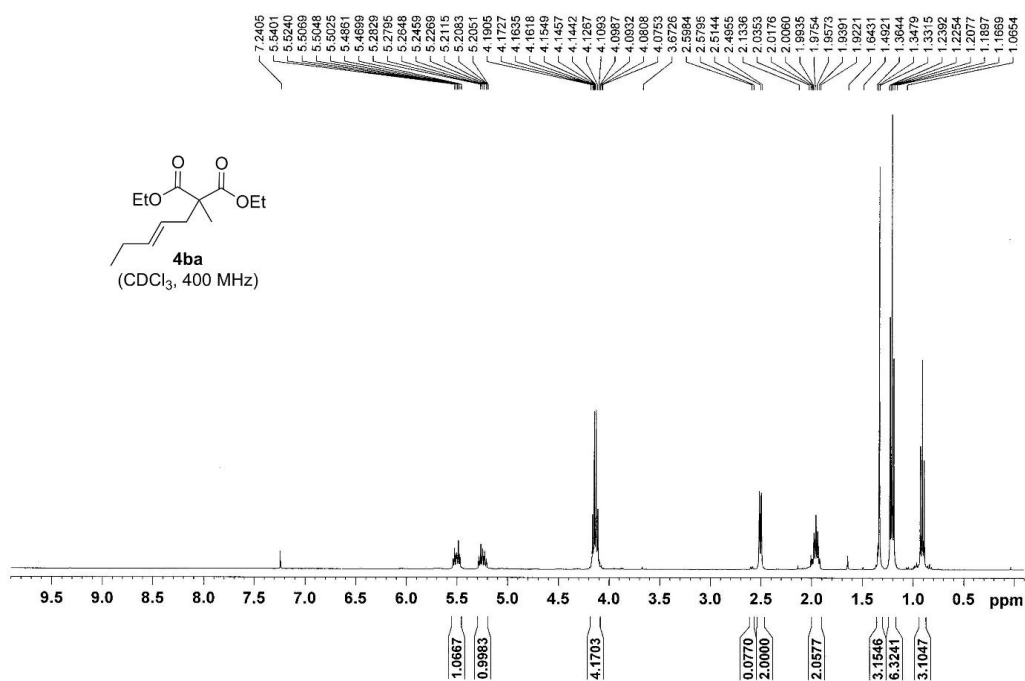


# <sup>13</sup>C-NMR of **4ag**

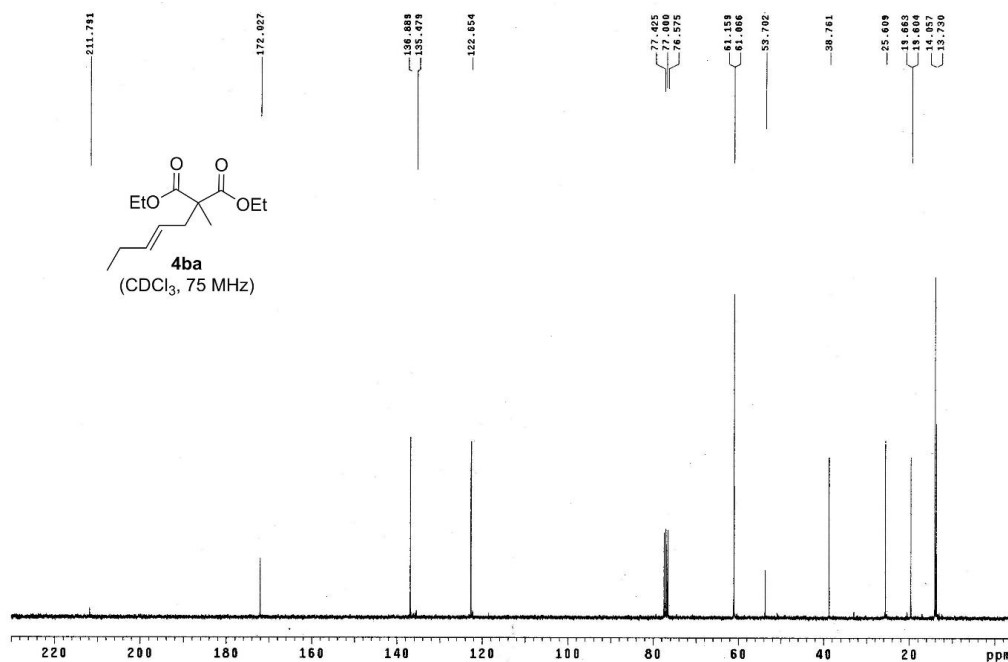




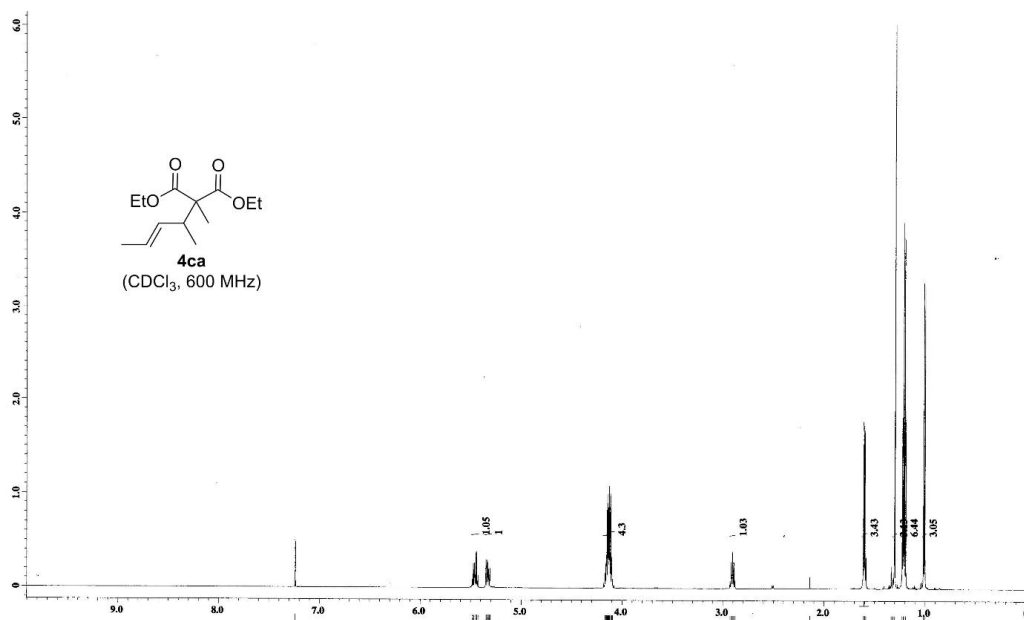
# <sup>1</sup>H-NMR of 4ba



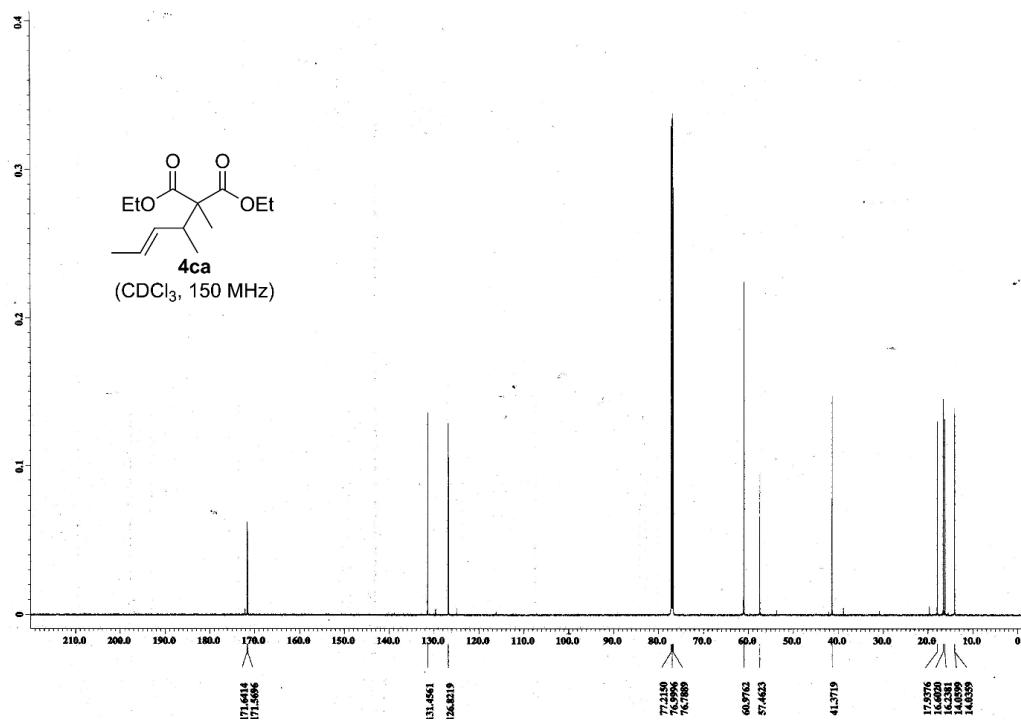
# <sup>13</sup>C-NMR of 4ba



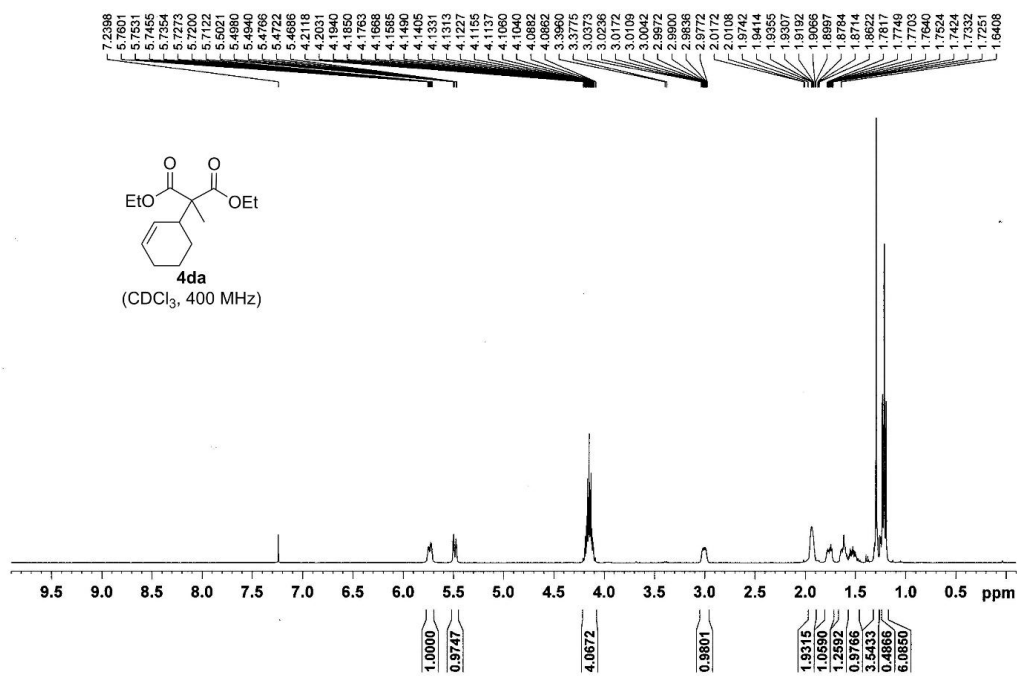
<sup>1</sup>H-NMR of **4ca**



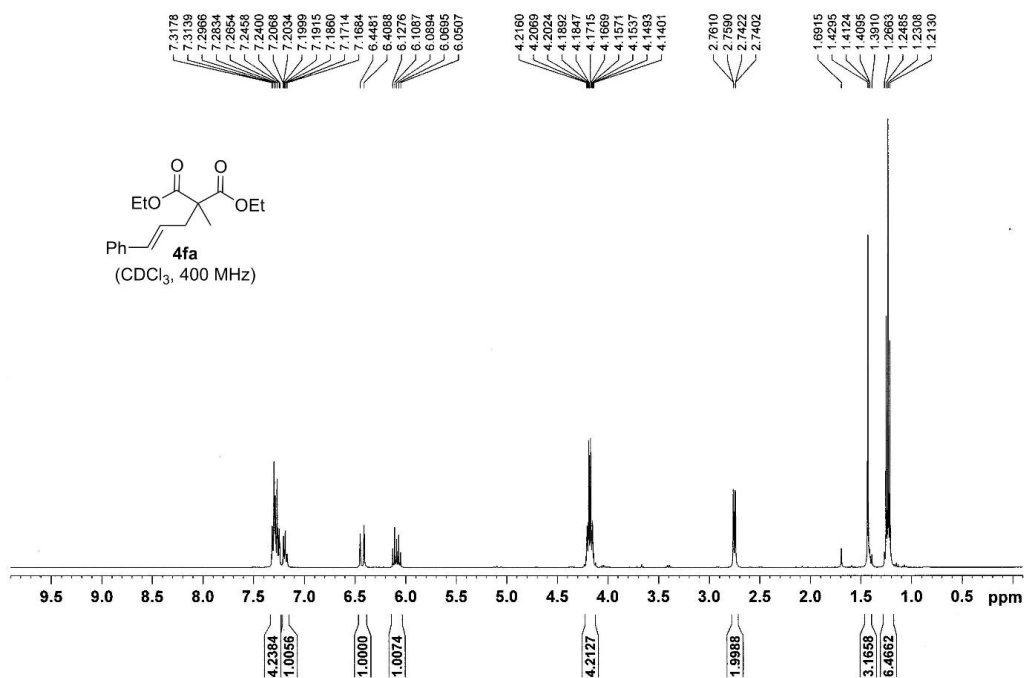
<sup>13</sup>C-NMR of **4ca**



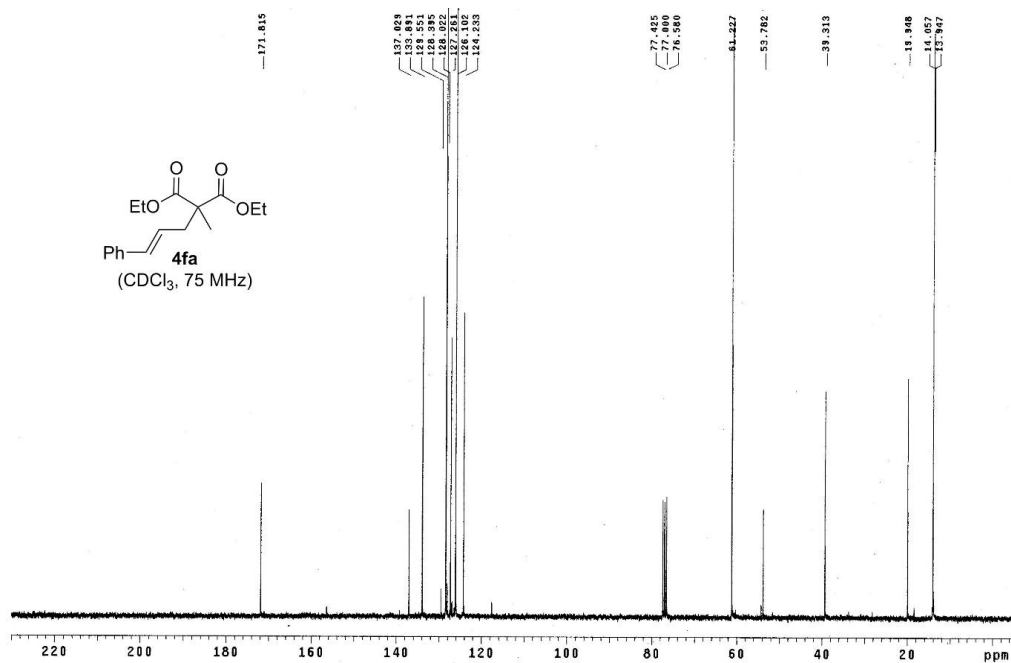
# <sup>1</sup>H-NMR of 4da



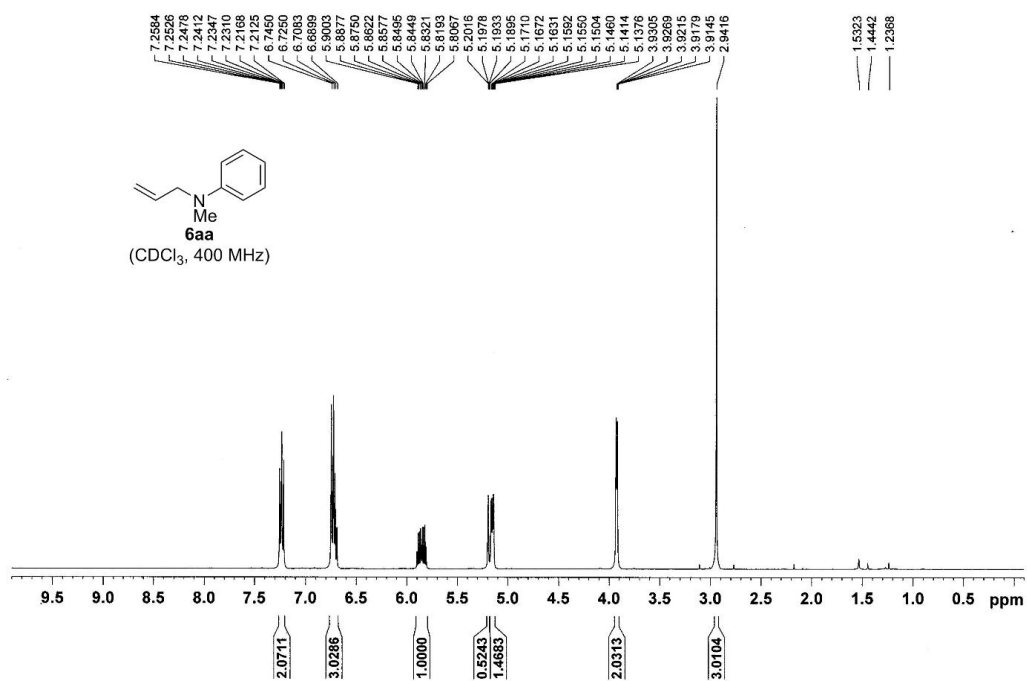
# <sup>1</sup>H-NMR of 4fa



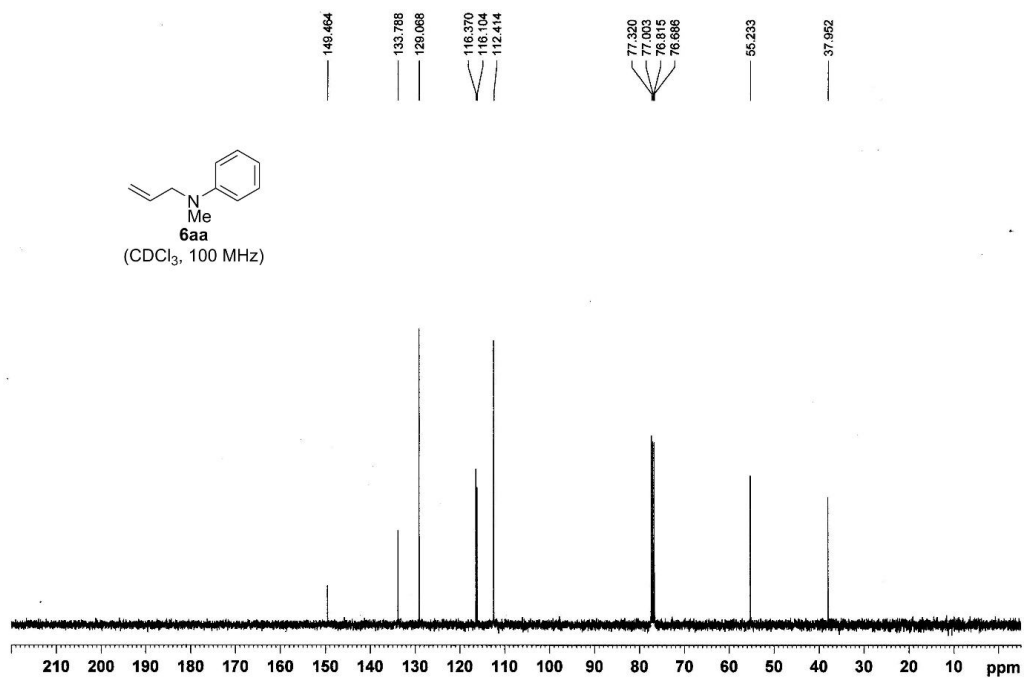
# <sup>13</sup>C-NMR of 4fa



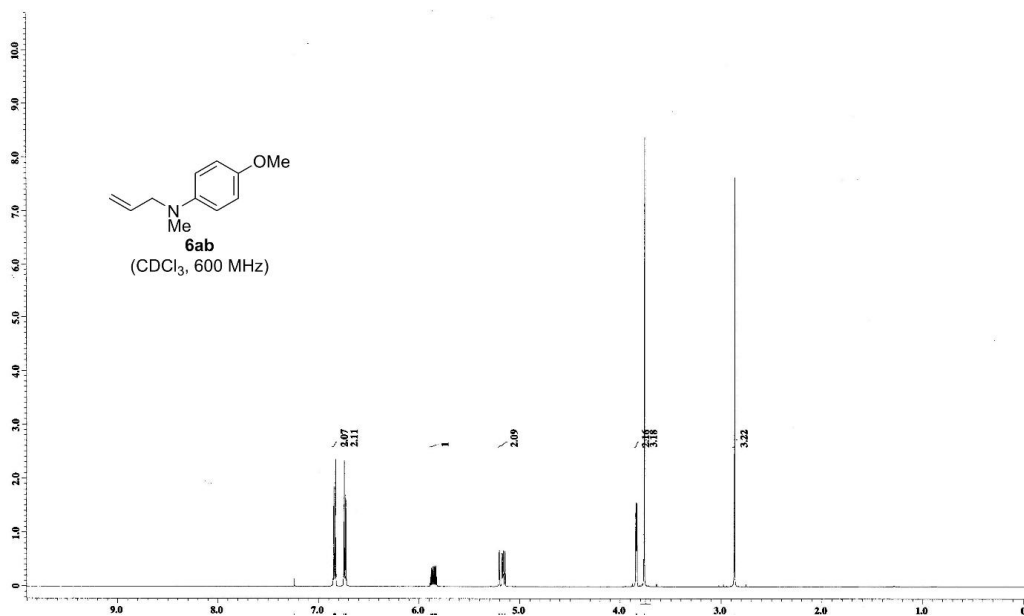
<sup>1</sup>H-NMR of **6aa**



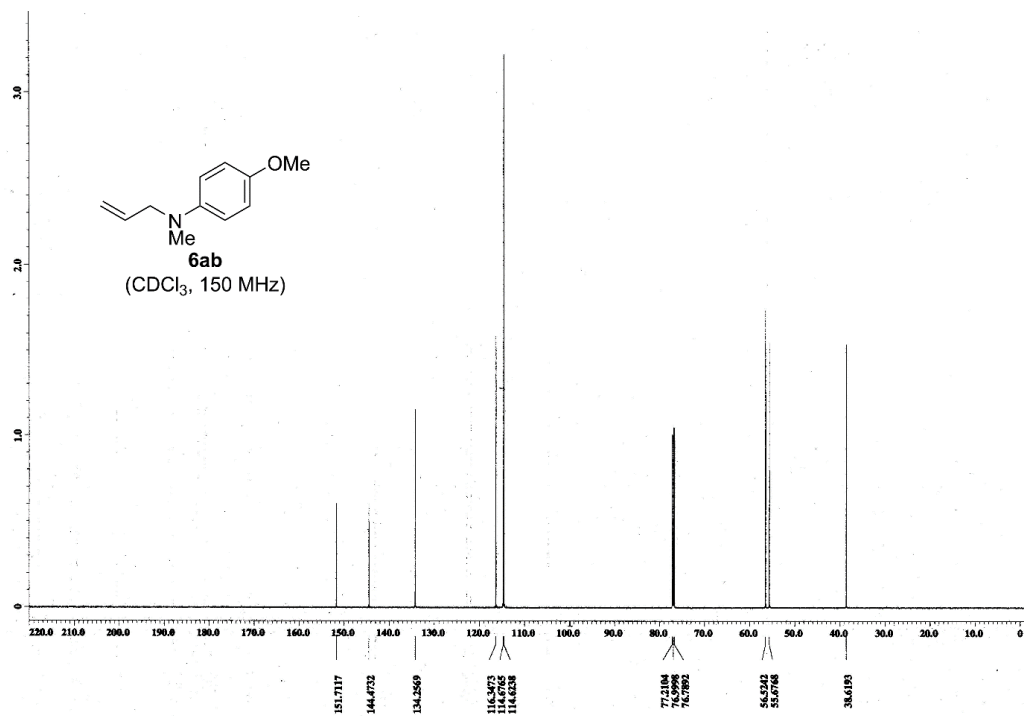
<sup>13</sup>C-NMR of **6aa**



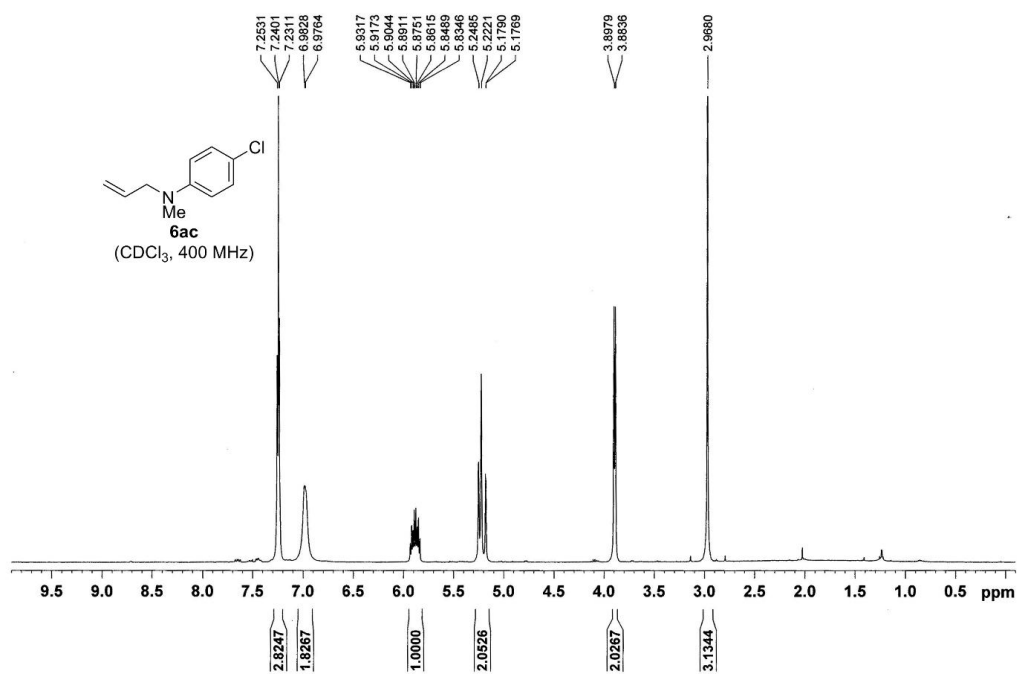
<sup>1</sup>H-NMR of **6ab**



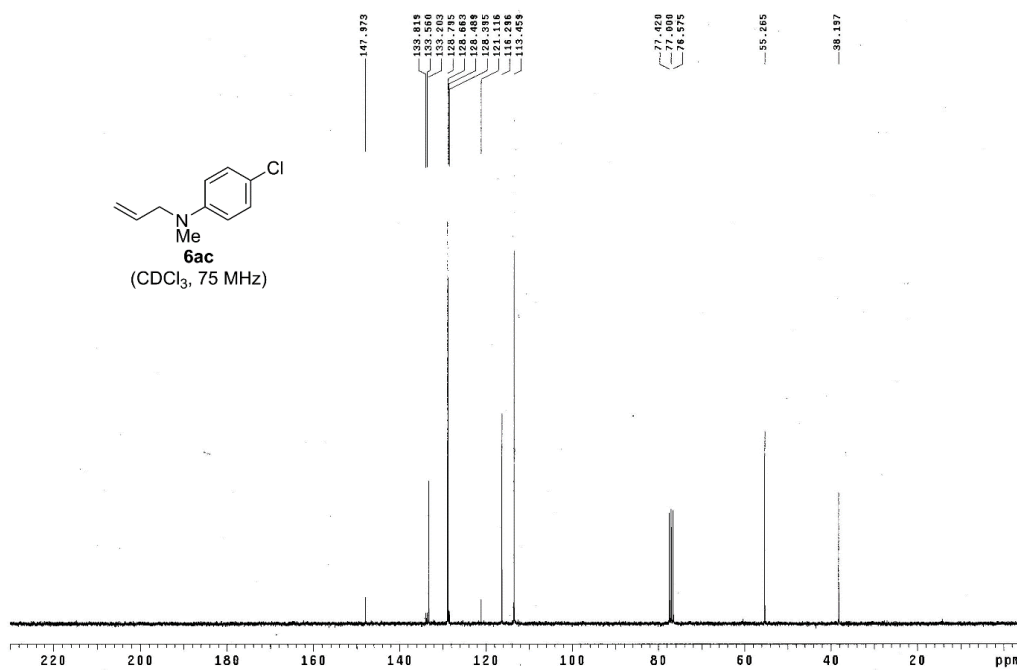
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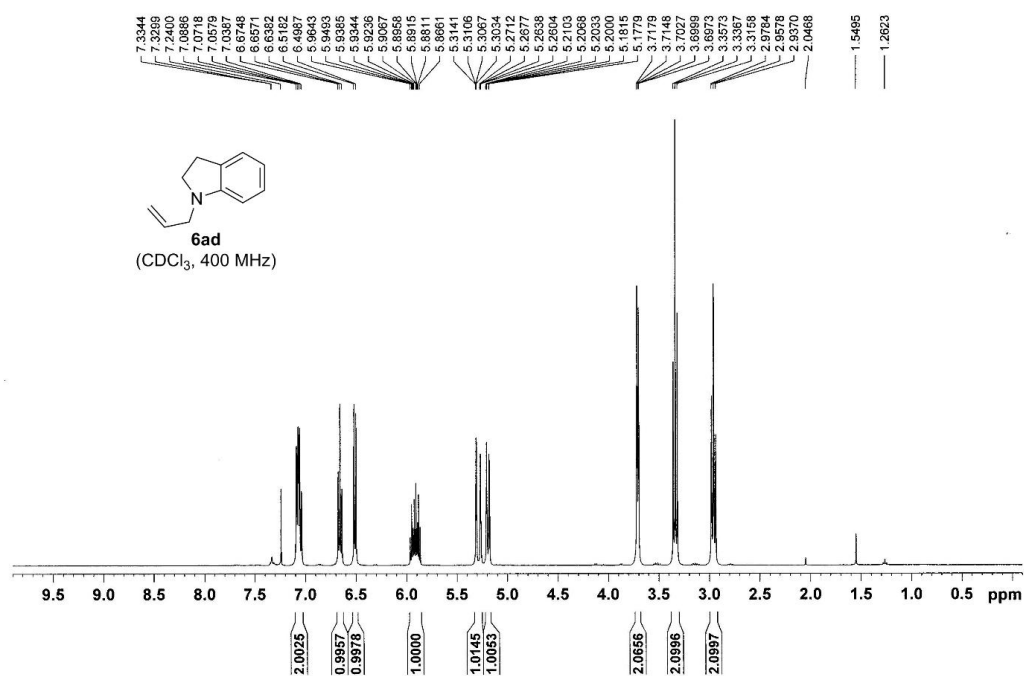
<sup>1</sup>H-NMR of **6ac**



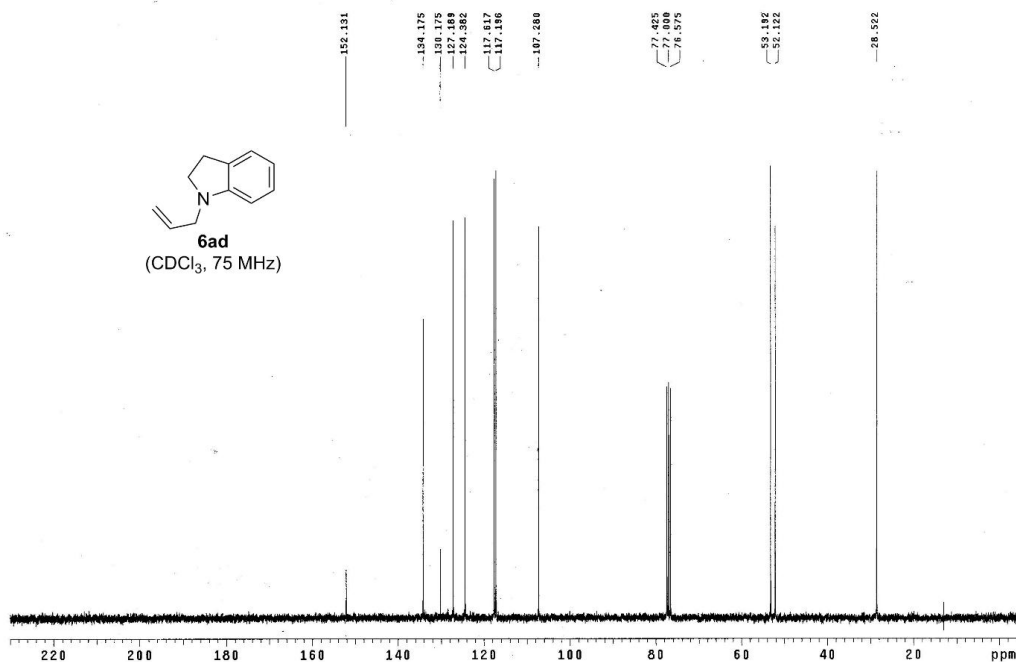
<sup>13</sup>C-NMR of **6ac**



# <sup>1</sup>H-NMR of 6ad

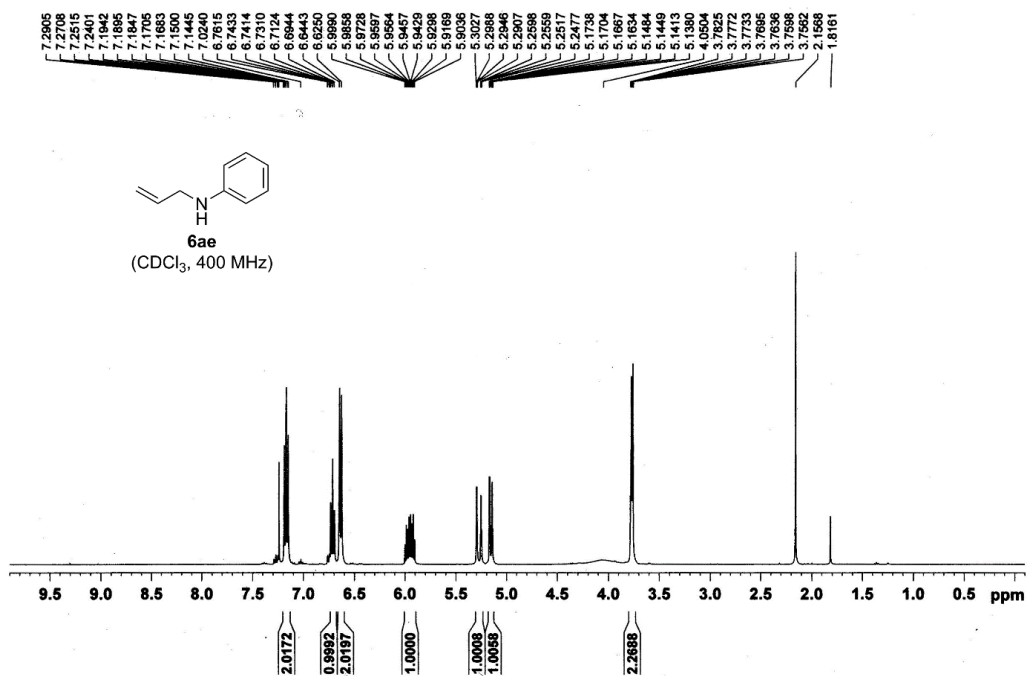


# <sup>13</sup>C-NMR of 6ad

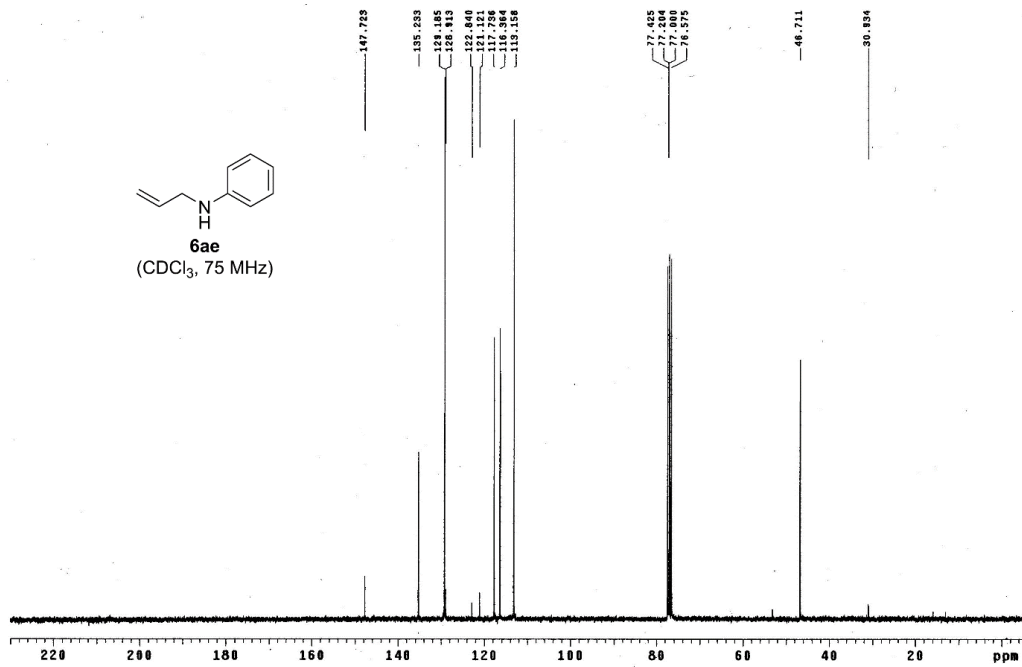




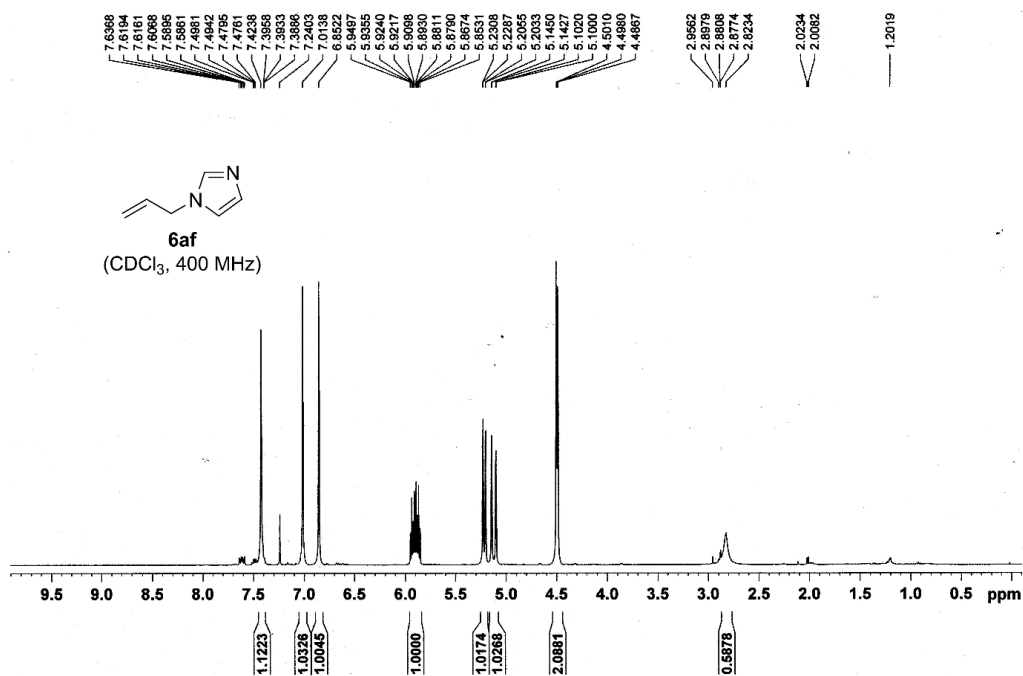
<sup>1</sup>H-NMR of **6ae**



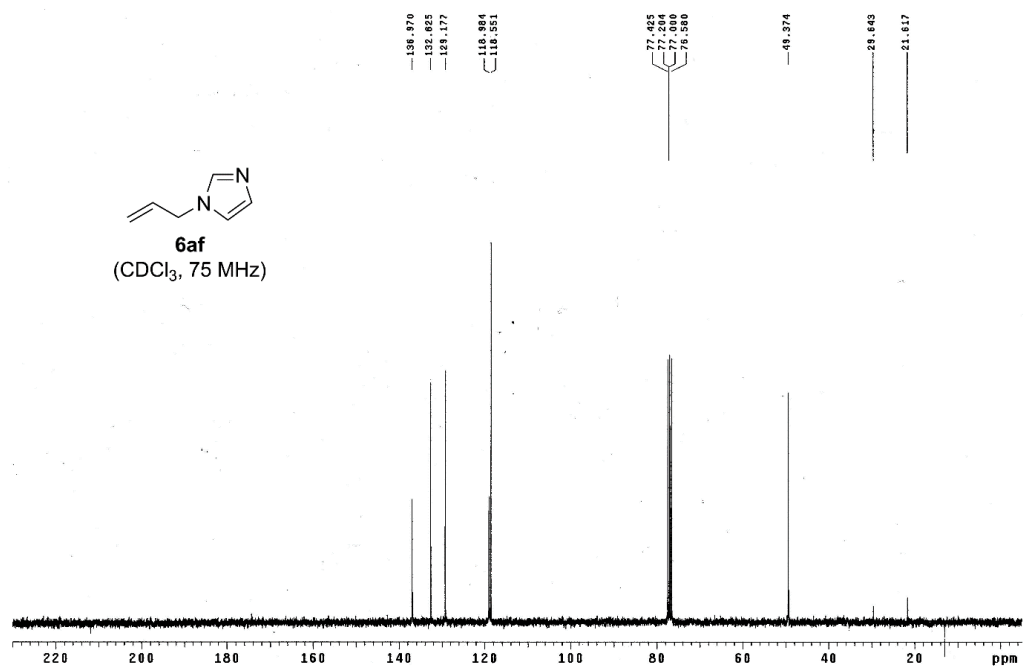
<sup>13</sup>C-NMR of **6ae**



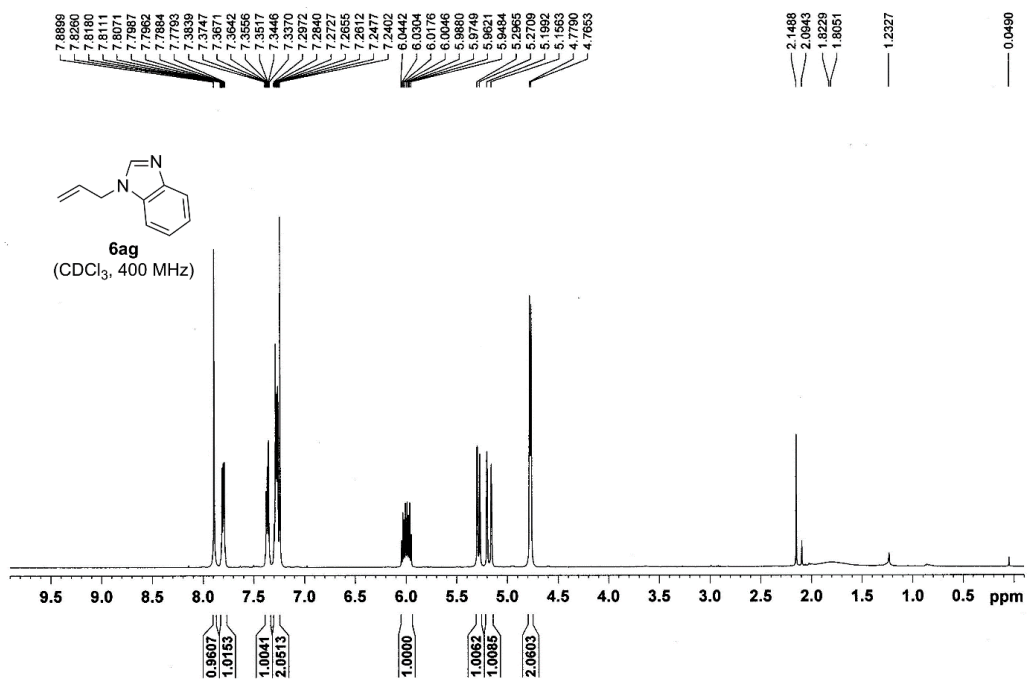
<sup>1</sup>H-NMR of **6af**



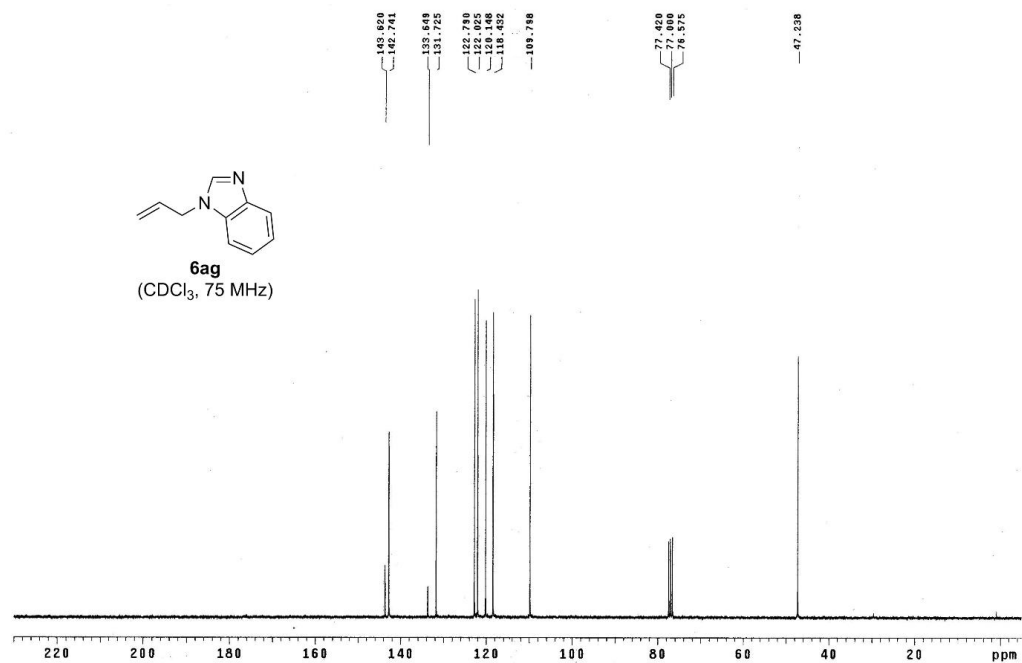
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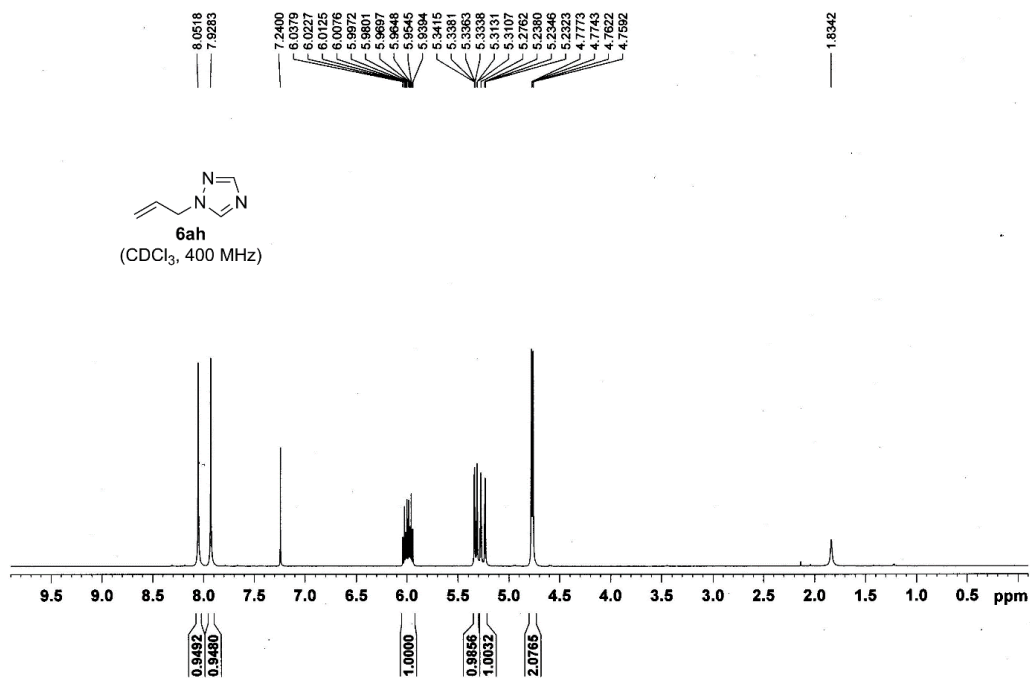
<sup>1</sup>H-NMR of **6ag**



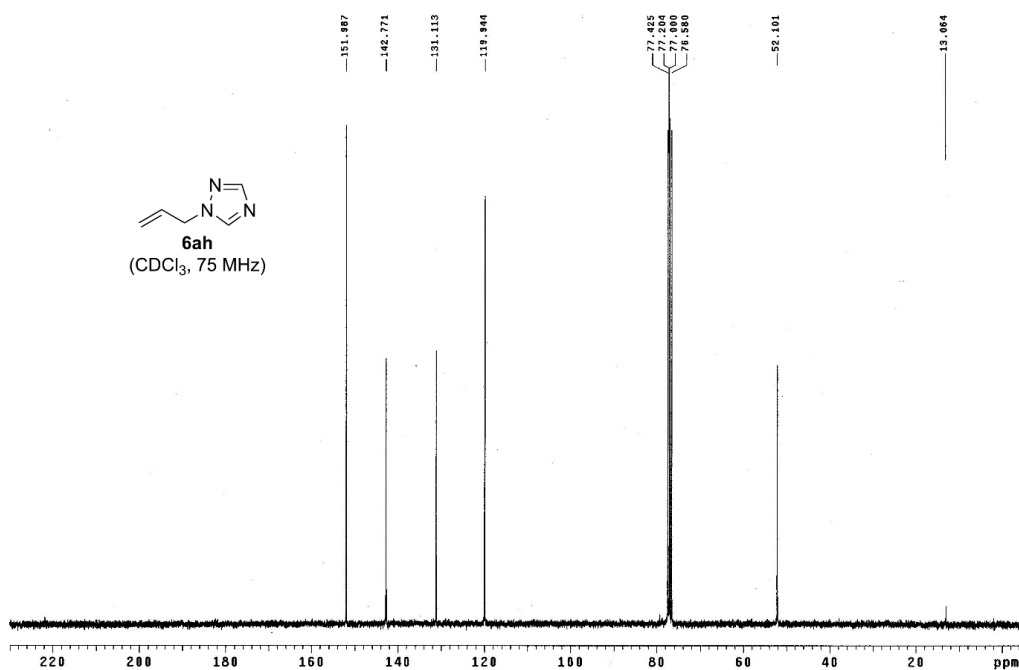
<sup>13</sup>C-NMR of **6ag**



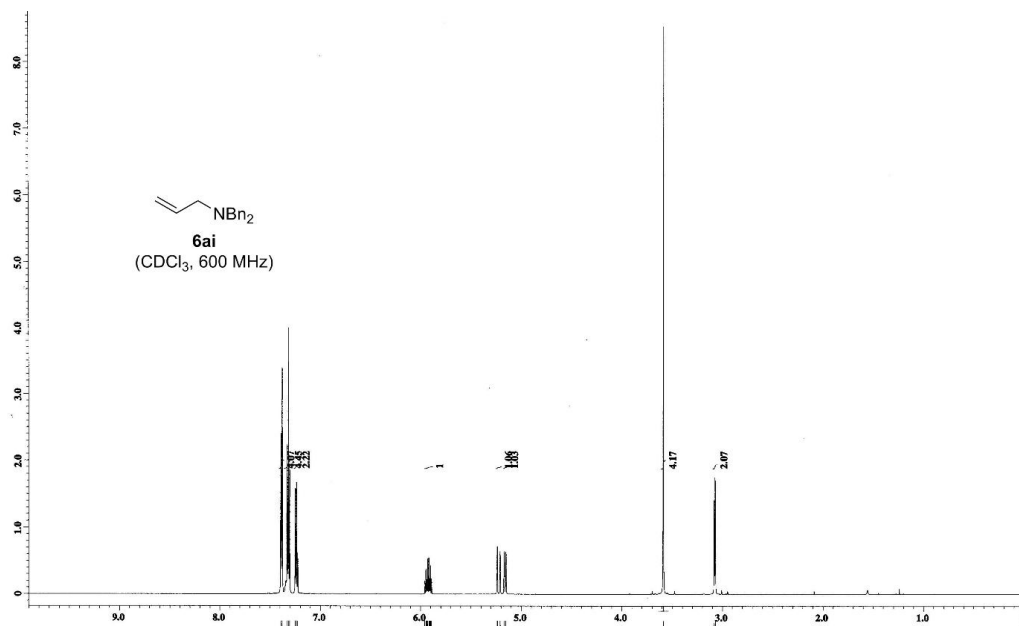
<sup>1</sup>H-NMR of **6ah**



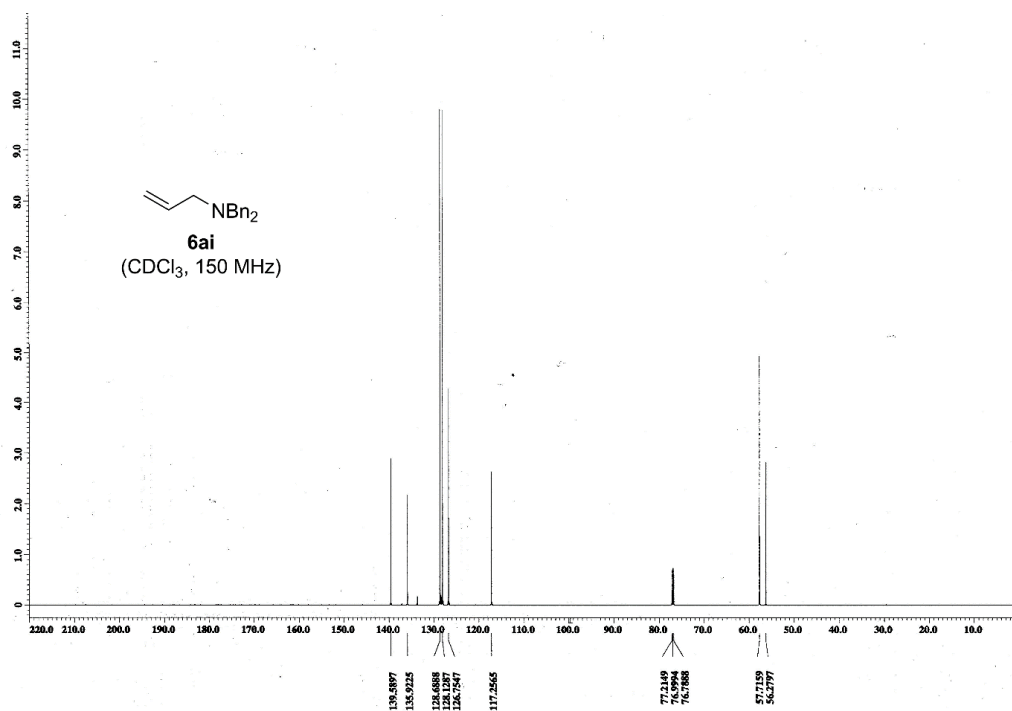
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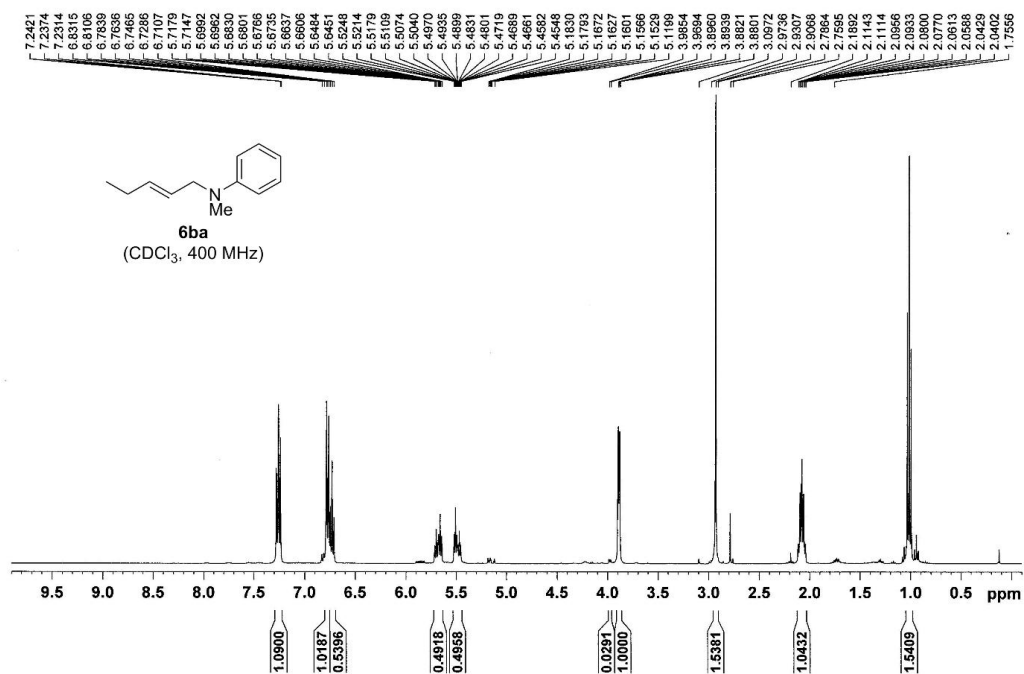
<sup>1</sup>H-NMR of **6ai**



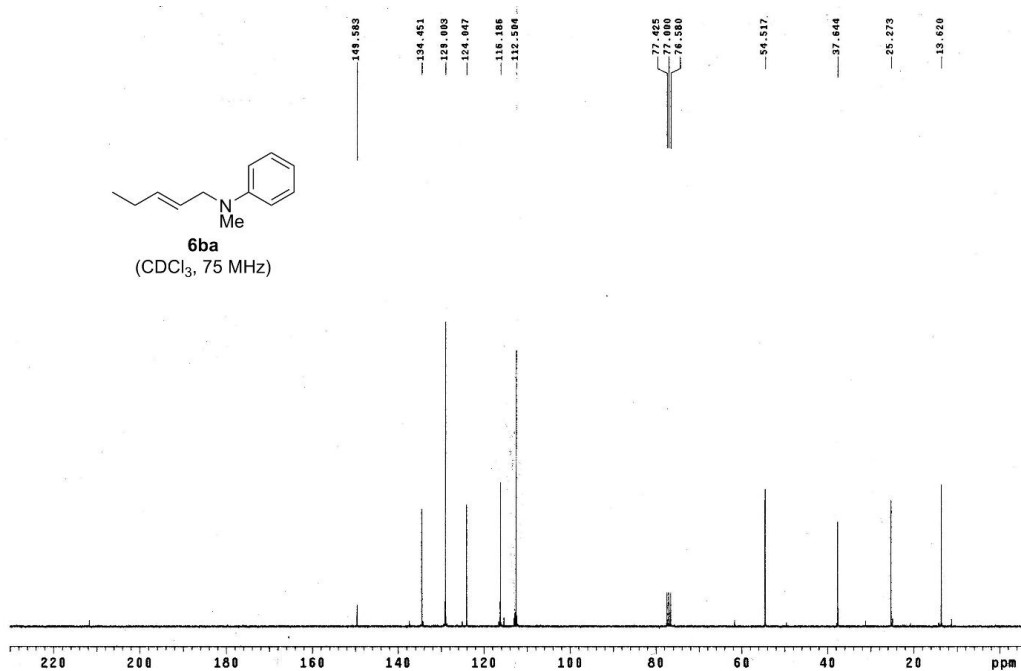
<sup>13</sup>C-NMR of **6ai**



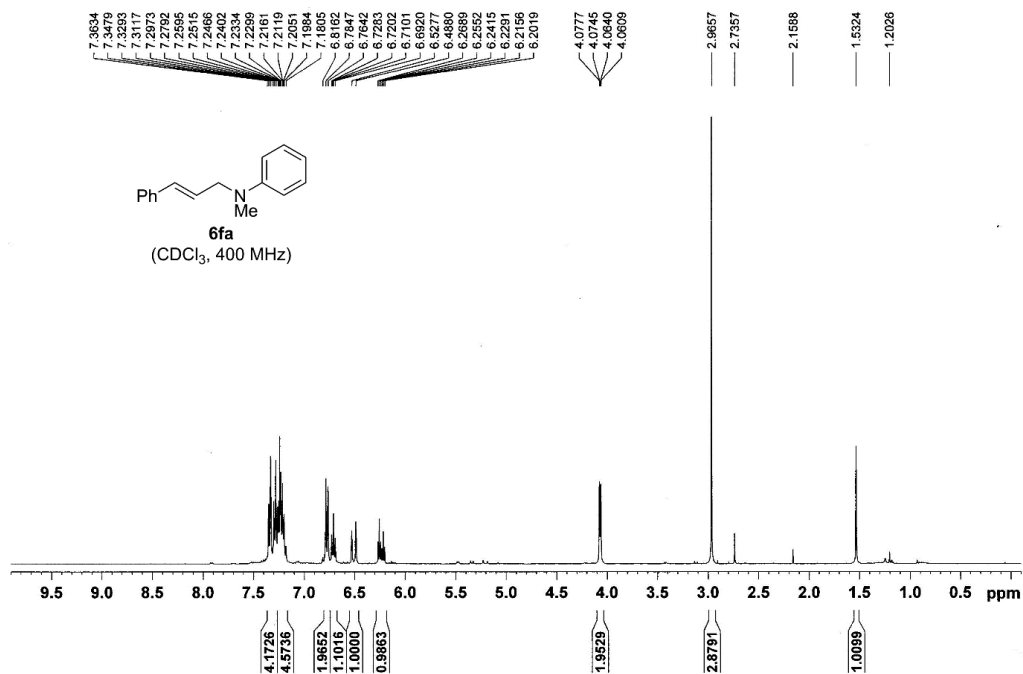
# <sup>1</sup>H-NMR of 6ba



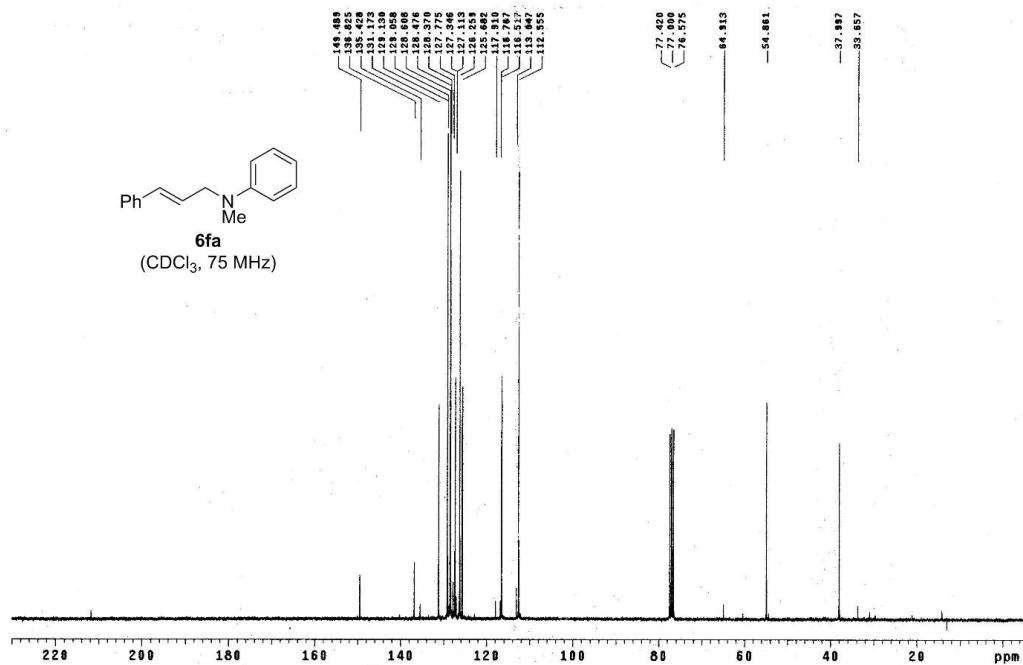
# <sup>13</sup>C-NMR of 6ba



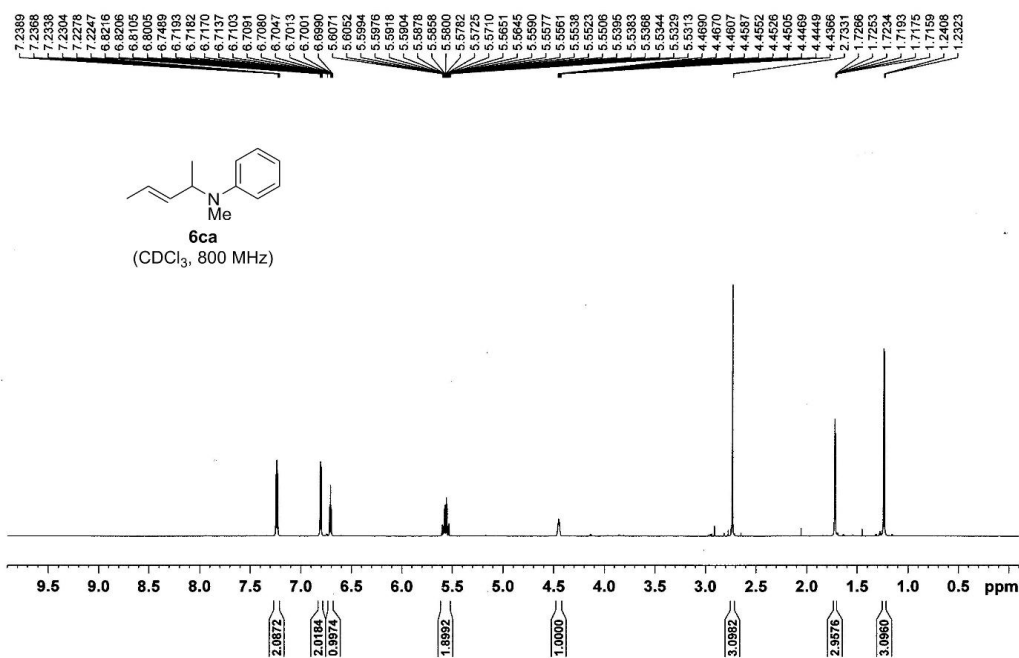
<sup>1</sup>H-NMR of **6fa**



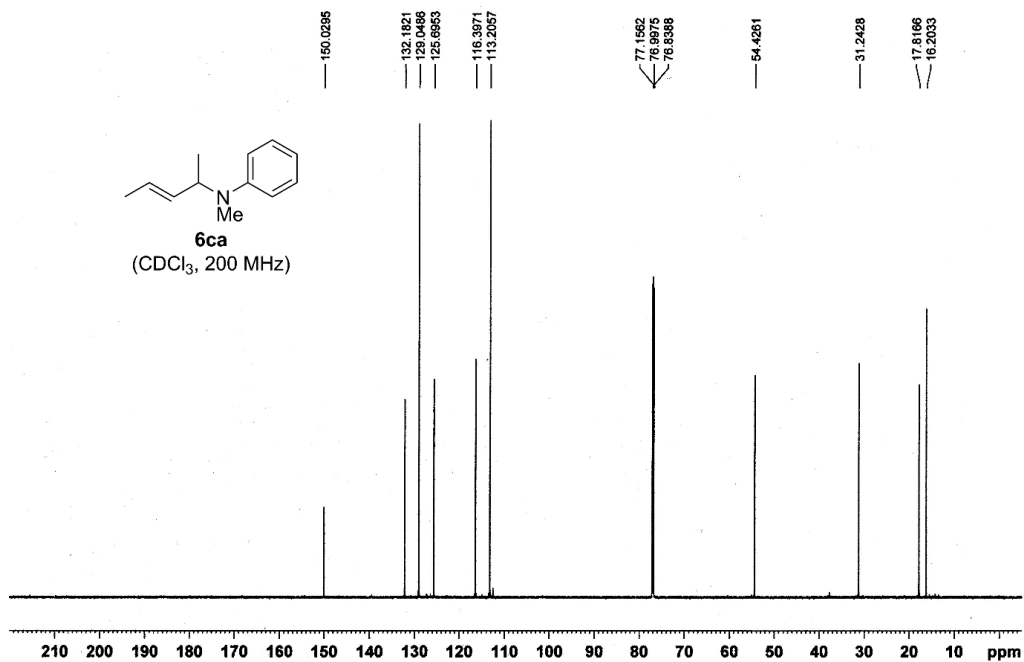
<sup>13</sup>C-NMR of **6fa**



# <sup>1</sup>H-NMR of 6ca

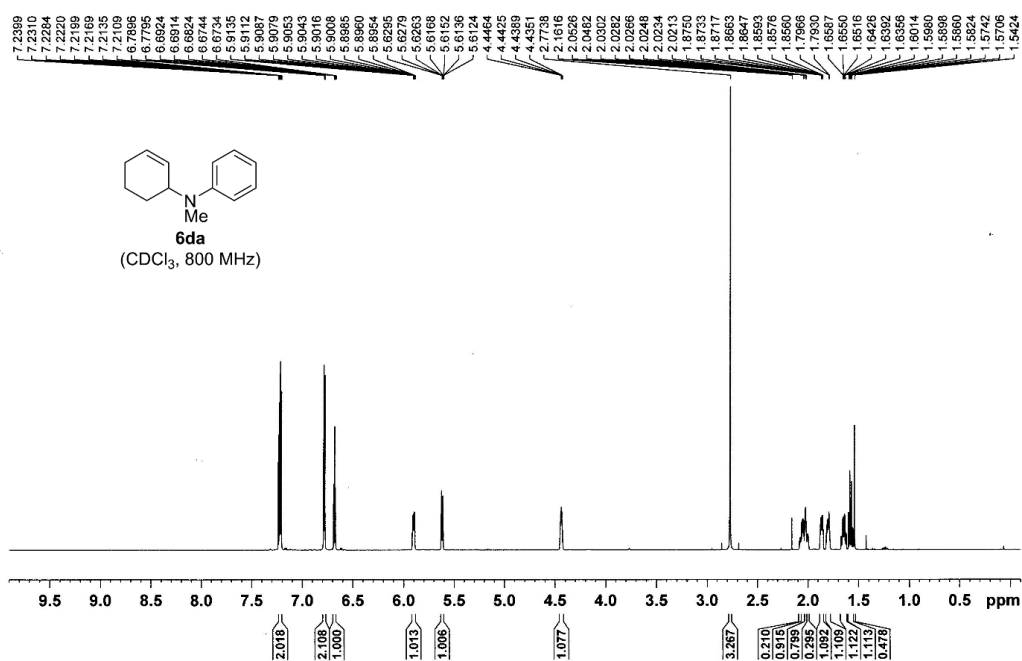


# <sup>13</sup>C-NMR of 6ca

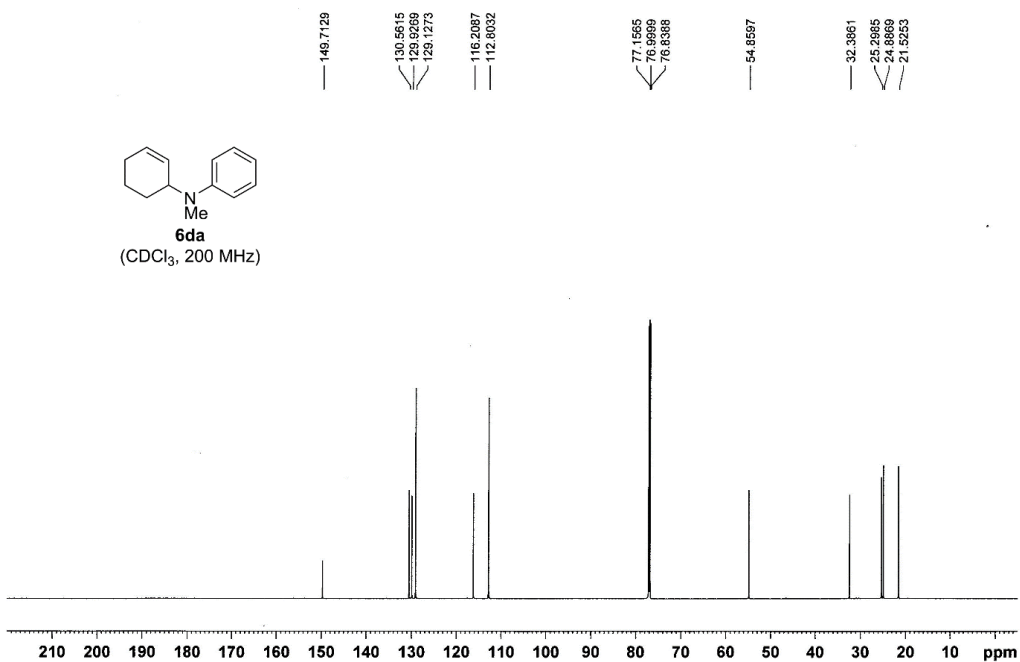




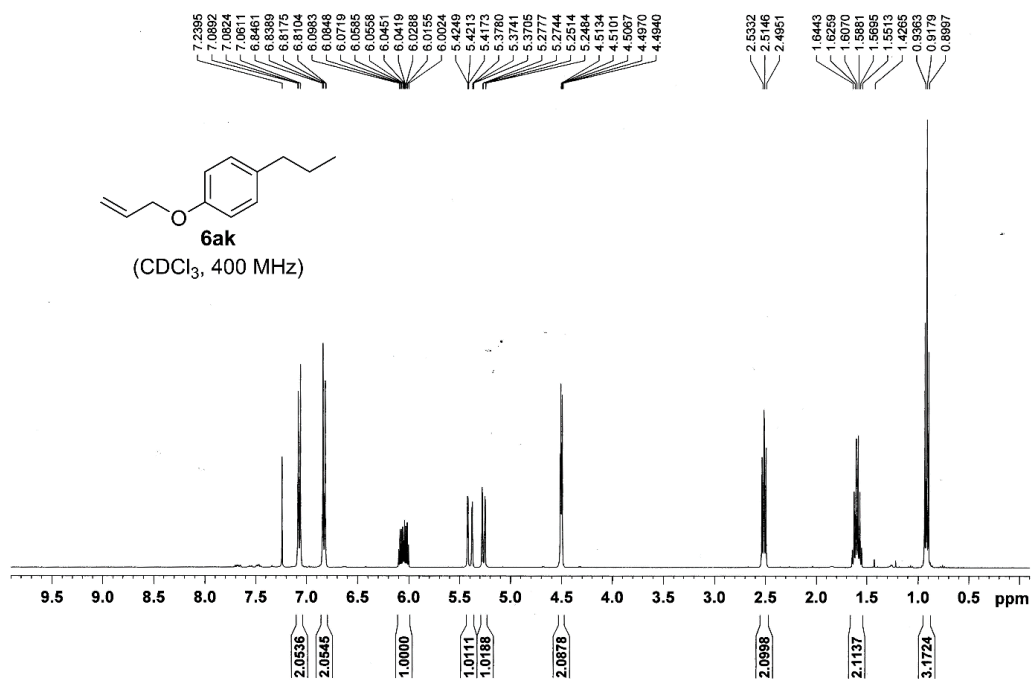
# <sup>1</sup>H-NMR of 6da



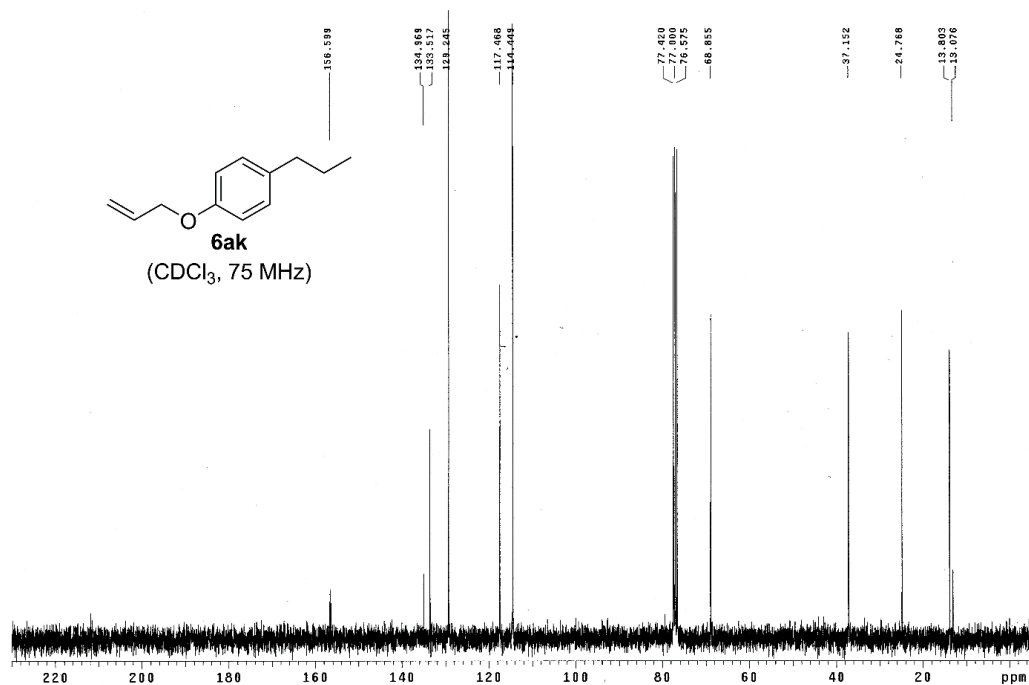
## <sup>13</sup>C-NMR of 6da



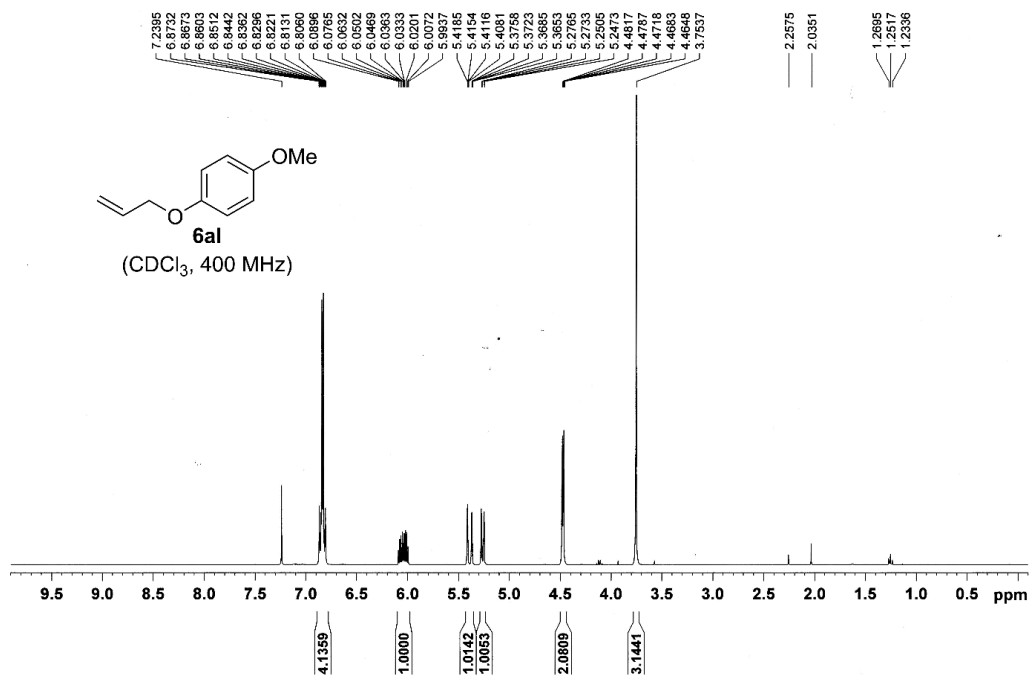
<sup>1</sup>H-NMR of **6ak**



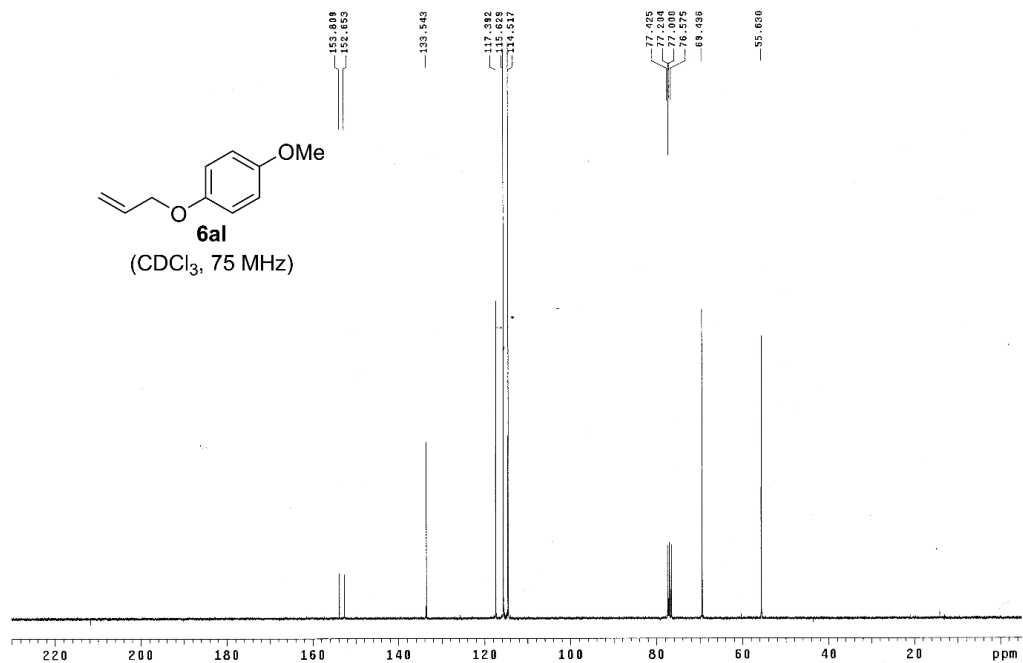
<sup>13</sup>C-NMR of **6ak**



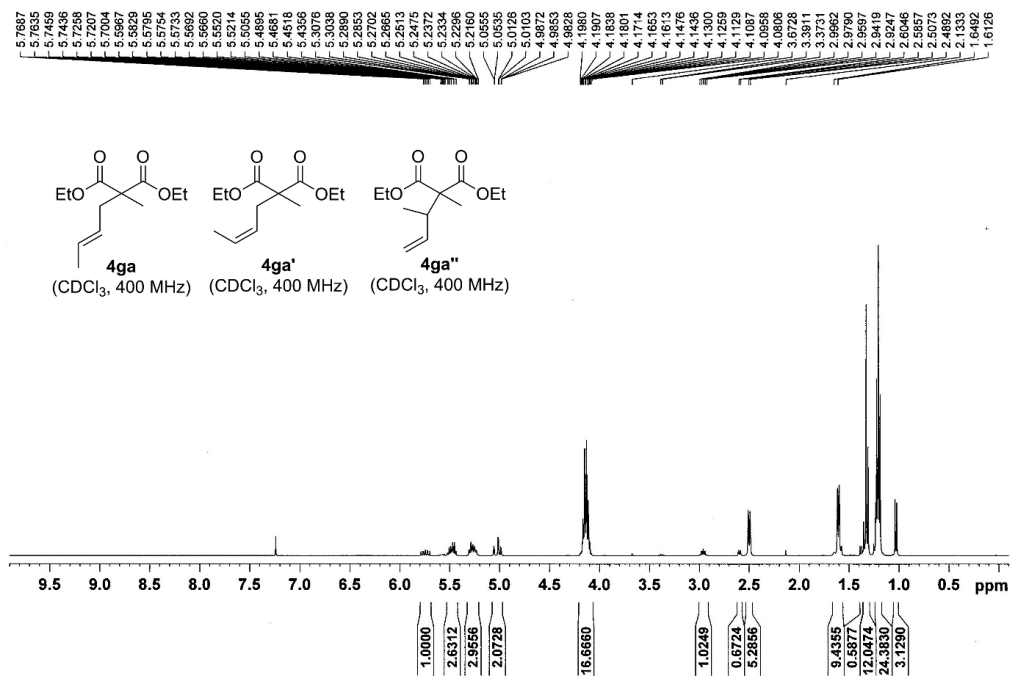
<sup>1</sup>H-NMR of **6al**



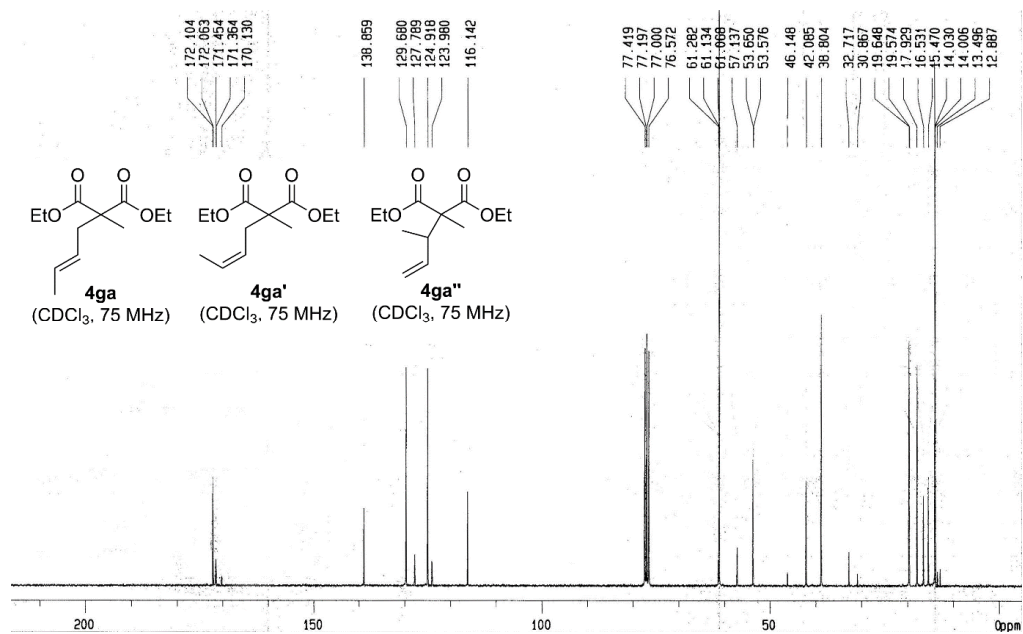
<sup>13</sup>C-NMR of **6al**



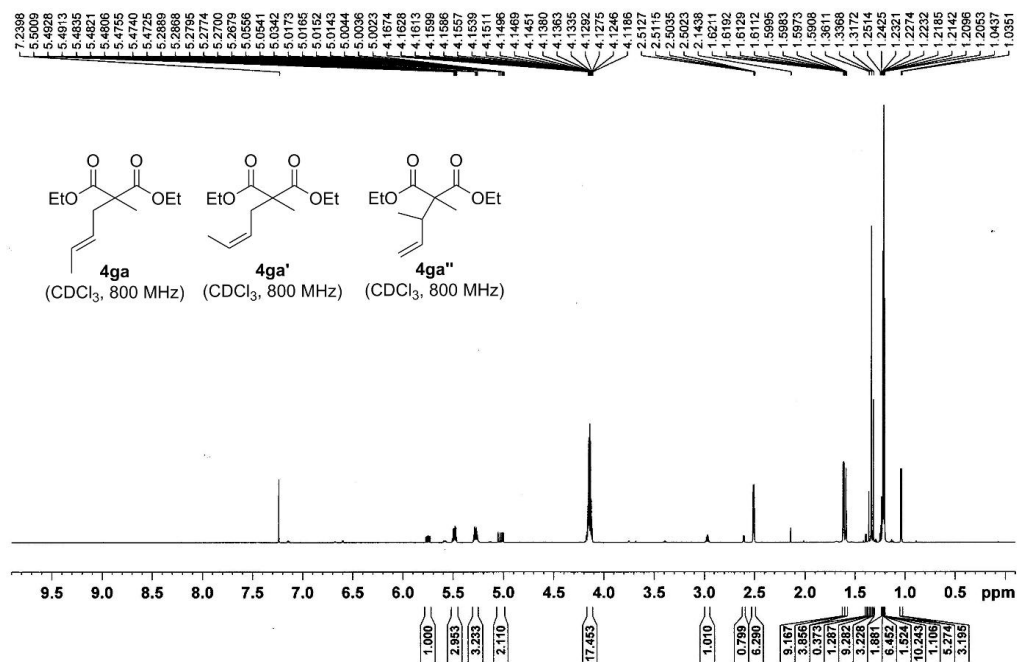
## VI-II. Allylation of 3a with the isomeric allylic alcohols



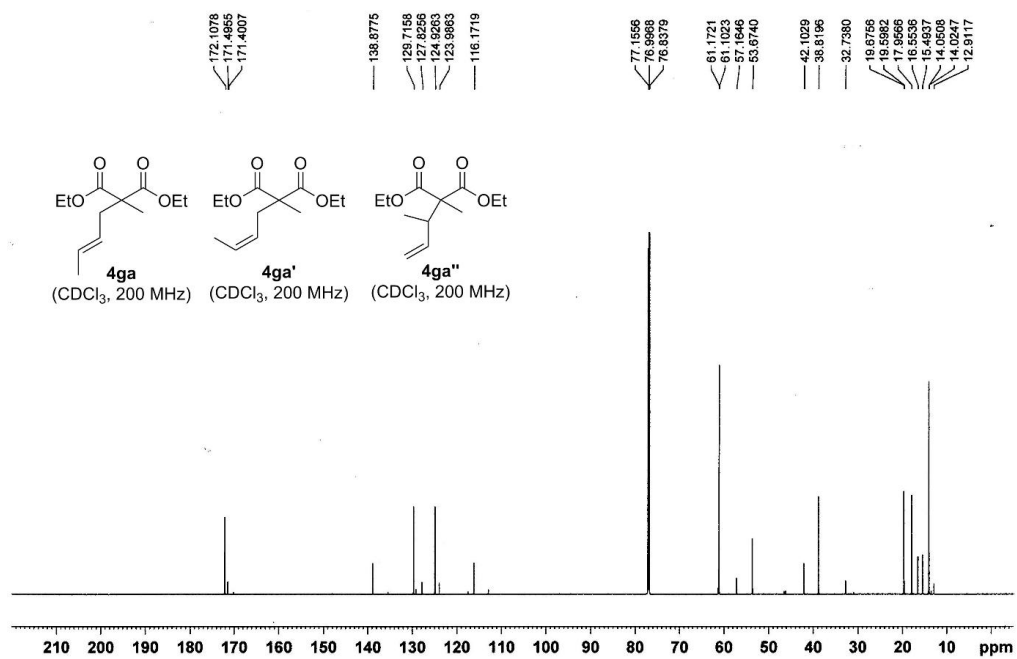
**Figure S1.**  $^1\text{H}$  NMR spectra of regioisomeric mixture obtained from the reaction with **2g**



**Figure S2.**  $^{13}\text{C}$  NMR spectra of regioisomeric mixture obtained from the reaction with **2g**



**Figure S3.**  $^1\text{H}$  NMR spectra of regioisomeric mixture obtained from the reaction with **2h**

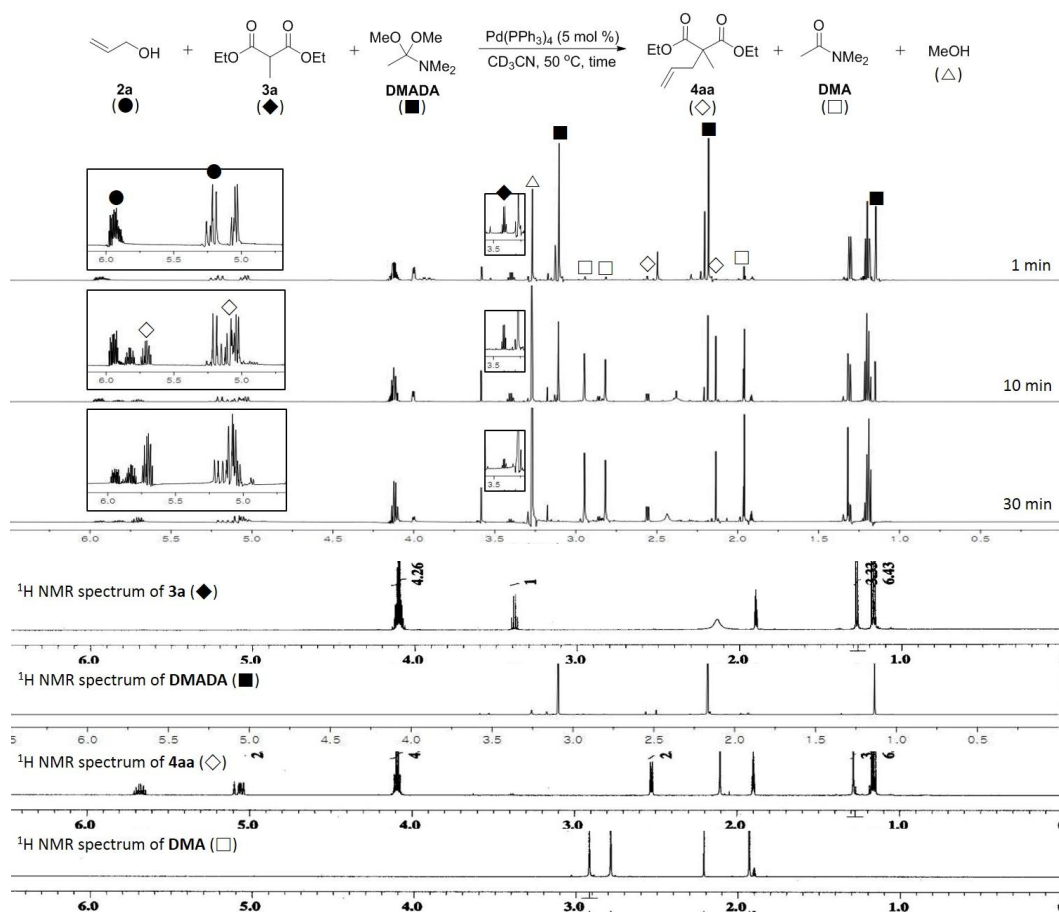


**Figure S4.**  $^{13}\text{C}$  NMR spectra of the regioisomeric mixture obtained from the reaction with **2h**

**2h**

### VI-III. $^1\text{H}$ NMR spectroscopy study

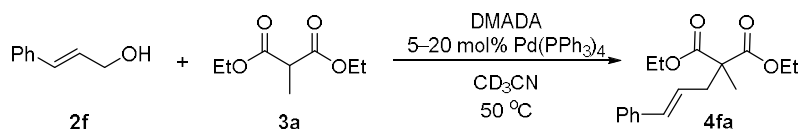
반응 기전을 더 이해하기 위해, 우리는 *in situ*  $^1\text{H}$  NMR spectroscopy analysis를 수행했다. *N,N*-dimethylacetamide dimethylacetal (DMADA, **1**, 2.0 mmol), allylic alcohol **2a** (2.0 mmol), malonate **3a** (1.0 mmol)가  $\text{CD}_3\text{CN}$  (2 mL)에서 질소 기류하의  $50\text{ }^\circ\text{C}$ 에서 반응이 진행되었다. Figure S5에 나타낸 것처럼, *N,N*-dimethylacetamide (DMA) and MeOH가 product **4aa**가 생성됨에 따라 증가되었다. 생성 가능한 부산물인 allyl methyl ether나 diallyl ether는 NMR-monitoring에서 관찰되지 않았다. 이런 결과들과 isomeric allylic alcohols을 사용한 실험결과 (see Scheme 2)를 종합하여, 우리는 Scheme 3에서와 같은 allylation 기전을 제시하였다.



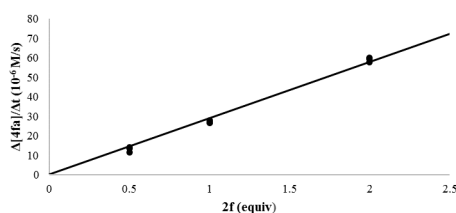
**Figure S5.** *In situ*  $^1\text{H}$  NMR spectra of the reaction mixture ( $\text{CD}_3\text{CN}$ , 600 MHz)

## VI-IV. Kinetic Experiment

cinnmayl alcohol **2f**과 diethyl methylmalonate **3a**에서 diethyl 2-cinnamyl-2-methylmalonate **4fa**이 생성될 때 초기 반응속도 (initial rate)를 측정: **2f** (27.4 mg, 0.2 mmol, 1.0 equiv), **3a** (36.3 mg, 0.2 mmol, 1.0 equiv), DMADA (29.6 mg, 0.2 mmol, 1.0 equiv), tetrakis(triphenylphosphine)palladium(0) (23.1 mg, 0.02 mmol, 10 mol%), CD<sub>3</sub>CN (1 mL, 0.2 M)에 녹여 질소 기류하의 조건과 50 °C에서 교반한다. 반응속도는 <sup>1</sup>H NMR spectroscopy를 이용하여 1,2-dibromoethane (75.1 mg, 0.4 mmol)를 internal standard로 하여 측정한다. 초기 반응속도는 reactant의 농도에 따라 측정된다. **4fa**가 40% 이하로 생성될 때 선형 기울기를 얻는다.

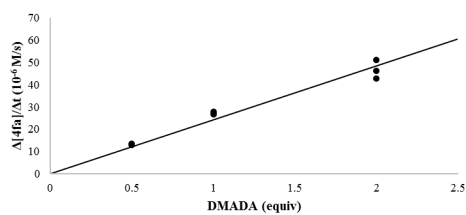


$$\text{Reaction rate} = k[\mathbf{2f}][\text{DMADA}][\text{Pd}][\mathbf{3a}]^0$$



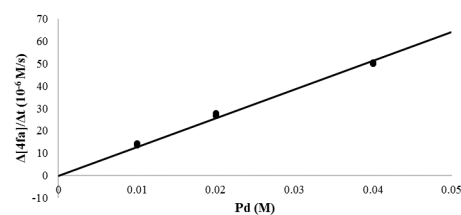
Entry	Cinnmayl alcohol (M)	Diethyl methylmalonate (M)	DMADA (M)	Pd(PPh <sub>3</sub> ) <sub>4</sub> (M)	Δ[ <b>4fa</b> ]/Δt (10 <sup>-6</sup> M/s)
1	0.1	0.2	0.2	0.02	11.57
2	0.1	0.2	0.2	0.02	13.57
3	0.1	0.2	0.2	0.02	14.02
4	0.2	0.2	0.2	0.02	26.55
5	0.2	0.2	0.2	0.02	26.82
6	0.2	0.2	0.2	0.02	27.87
7	0.4	0.2	0.2	0.02	59.32
8	0.4	0.2	0.2	0.02	57.67
9	0.4	0.2	0.2	0.02	59.82

**Figure S6.** Initial rate of allylation of **3a** with **2f** concentration.



Entry	Cinnmayl alcohol (M)	Diethyl methylmalonate (M)	DMADA (M)	Pd(PPh <sub>3</sub> ) <sub>4</sub> (M)	Δ[4fa]/Δt (10 <sup>-6</sup> M/s)
1	0.2	0.2	0.1	0.02	13.13
2	0.2	0.2	0.1	0.02	12.87
3	0.2	0.2	0.1	0.02	13.42
4	0.2	0.2	0.2	0.02	26.55
5	0.2	0.2	0.2	0.02	26.82
6	0.2	0.2	0.2	0.02	27.87
7	0.2	0.2	0.4	0.02	51.13
8	0.2	0.2	0.4	0.02	46.18
9	0.2	0.2	0.4	0.02	42.67

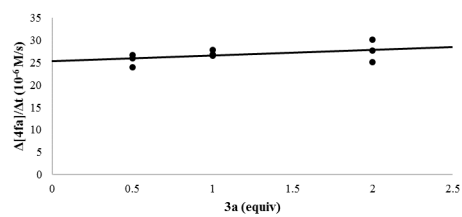
**Figure S7.** Initial rate of allylation of **3a** of with DMADA concentration.



Entry	Cinnmayl alcohol (M)	Diethyl methylmalonate (M)	DMADA (M)	Pd(PPh <sub>3</sub> ) <sub>4</sub> (M)	Δ[4fa]/Δt (10 <sup>-6</sup> M/s)
1	0.2	0.2	0.2	0.01	13.53
2	0.2	0.2	0.2	0.01	14.24
3	0.2	0.2	0.2	0.01	14.08
4	0.2	0.2	0.2	0.02	26.55
5	0.2	0.2	0.2	0.02	26.82
6	0.2	0.2	0.2	0.02	27.87
7	0.2	0.2	0.2	0.04	50.57
8	0.2	0.2	0.2	0.04	49.97
9	0.2	0.2	0.2	0.04	50.15

**Figure S8.** Initial rate of allylation of **3a** with Pd concentration.





Entry	Cinnmayl alcohol (M)	Diethyl methylmalonate (M)	DMADA (M)	Pd(PPh <sub>3</sub> ) <sub>4</sub> (M)	$\Delta[4fa]/\Delta t$ ( $10^{-6}$ M/s)
1	0.2	0.1	0.2	0.02	23.98
2	0.2	0.1	0.2	0.02	26.70
3	0.2	0.1	0.2	0.02	26.02
4	0.2	0.2	0.2	0.02	26.55
5	0.2	0.2	0.2	0.02	26.82
6	0.2	0.2	0.2	0.02	27.87
7	0.2	0.4	0.2	0.02	28.63
8	0.2	0.4	0.2	0.02	25.05
9	0.2	0.4	0.2	0.02	30.13

**Figure S9.** Initial rate of allylation with **3a** concentration.

## VII. ABSTRACT

# Palladium-Catalyzed Allylation using Amide Acetal

**Jaehyun Jung**

**Department of Pharmacy**

**Pharmaceutical Chemistry Major**

**The Graduate School**

**Seoul National University**

Palladium-catalyzed allylation is an efficient synthetic method, which forms C-C and C-heteroatom bonds. Various modifications of this reaction as known as Tsuji-Trost reaction have been investigated, including applicable allylic substrates. In this type of allylation, allylic alcohols are not usually used as the allyl source because of its poor leaving ability. Instead, activated allylic alcohol derivatives, such as halides, acetates, and carbonates, are used. And also, methods activating hydroxyl groups using ligands, Lewis or Brønsted acids in certain conditions are widely known.

We successfully synthesized allylic compounds via *in situ* activation of hydroxyl groups of allylic alcohols using amide acetals. *N,N*-dimethylacetamide dimethyl acetal (DMADA), one of the amide acetals, was employed as an activator for allylation with palladium catalyst ( $\text{Pd}(\text{PPh}_3)_4$ ) and various nucleophiles. Through this developed reaction, we got allylic compounds in high yield under mild conditions. And various nucleophiles including

carbon nucleophiles, nitrogen and oxygen nucleophiles underwent allylation successfully. In addition to this study, kinetic experiment was taken to understand mechanism of this new reaction.

**Keywords : Amide acetal, Allylation, Palladium, Synthetic methods**

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## 감사의 글

석사기간 동안 많은 관심과 가르침을 주신 김상희 지도교수님께 깊은 감사드립니다. 바쁘신 와중에도 귀중한 시간을 내주신 이지우 교수님, 정낙신 교수님께도 고개 숙여 감사의 말씀드립니다.

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